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

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

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**Abstract**

*Background*: To investigate whether chronic opioid therapy is associated with a higher risk of cancer among non-cancer 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 multivariable time-dependent Cox regression model, the risk of cancer in chronic opioid users was 1.20-fold higher than that in controls (hazard ratio [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.

*Conclusion*: Chronic opioid therapy was associated with an increased risk of cancer among non-cancer 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 non-cancer 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 cancer patients, as their immune system is already impaired (17-20). However, non-cancer 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 non-cancer patients with chronic pain may increase their risk of cancer. Most previous studies have focused only on the effect of chronic opioid use in cancer patients (23,24), and the relationship between chronic opioid use and cancer risk in non-cancer patients remains controversial.

Therefore, this study aimed to investigate whether chronic opioid therapy is associated with a higher risk of cancer in non-cancer 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 one 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 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 one million individuals until 2015.

### *Ethical statement*

The protocol of this study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (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, 10$^{th}$ 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: (1) demographic information (age and sex); (2) socioeconomic information (income level in deciles and place of residence in 2010 [Seoul, metropolitan cities, or others]); (3) Charlson's comorbidity index, which was calculated using the registered ICD-10 diagnostic codes between 2009 and 2010 in the NHIS database (Supplementary Table 1); (4) surgical history in 2010; and (5) chronic use of other analgesics for ≥90 days (nonsteroidal anti-inflammatory drugs, 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 chi-square test for categorical variables. The results of the tests are presented as means with standard deviations 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, 2011–2015. Exposure to chronic opioid therapy among both the chronic opioid users and controls in 2010 varied throughout the evaluation period (Supplementary Table 2).

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 multivariable adjustment. In particular, age, sex, income level, residence, Charlson's 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 hazard ratios (HRs) with 95% confidence intervals (CIs). All multivariable models of the entire cohort 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, Vienna, Austria). *P*-values <.05 were 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 multivariable 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 among controls (HR, 1.20; 95% CI, 1.15–1.25; $P$ <.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 multivariable 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 non-cancer 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 vascular endothelial growth factor, 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 et al. reported that chronic opioid use was associated with a second breast cancer event in primary breast cancer survivors (23), whereas Cronin-Fenton et al. reported that post-diagnosis 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 cancer patients 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 non-cancer pain (34). Since 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 multivariable models because they are not recorded in the NHIS database. Since 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. Additionally, 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, multivariable 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 non-cancer 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.

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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*-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) | |
| 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 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 |

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

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 | |
| 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 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 |

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

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

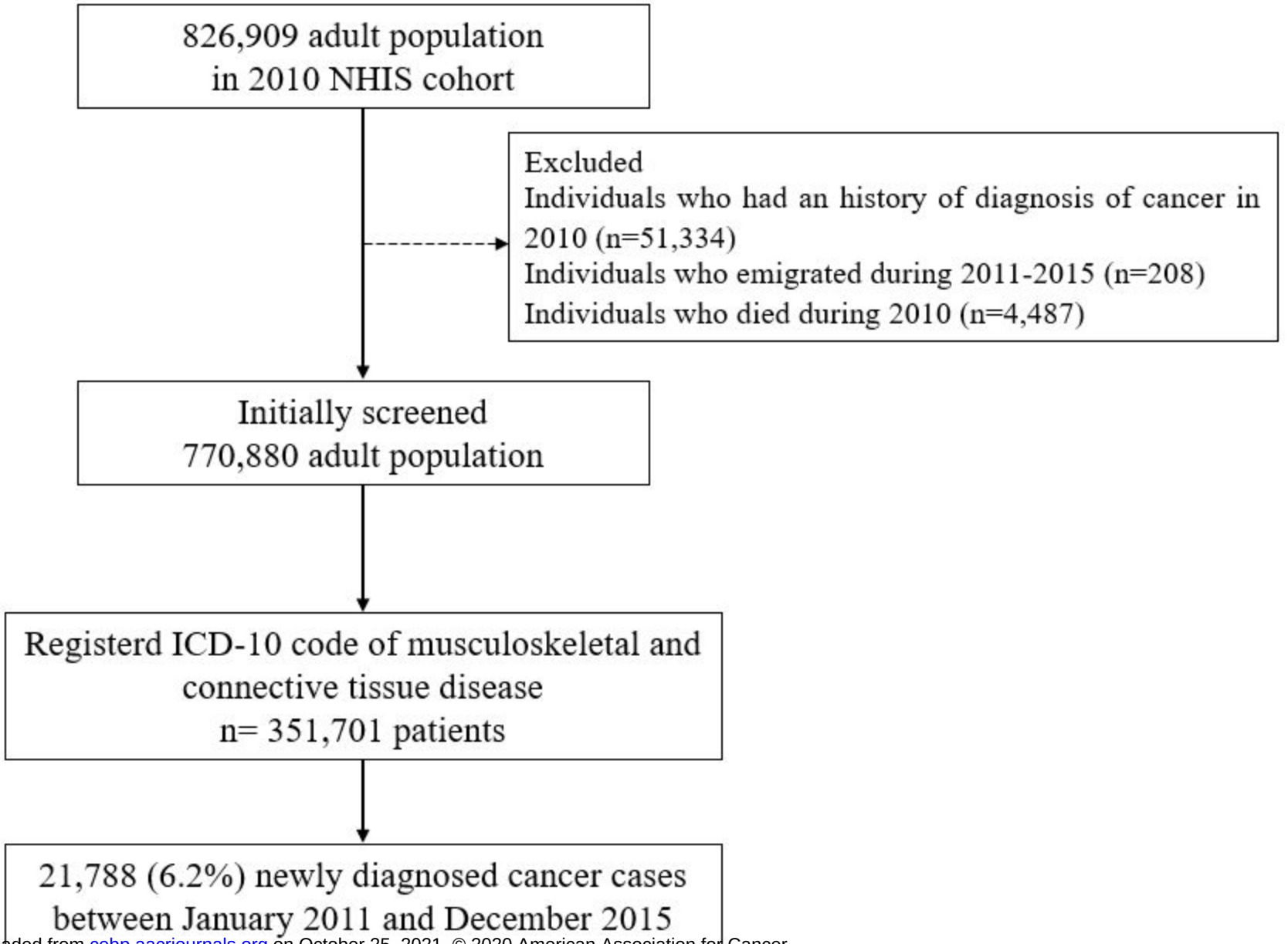
| Type of cancer | Multivariable model HR (95% CI) | *P*-value |
|---|---|---|
| Gastric cancer (C16) (n=1,748) | 0.89 (0.76, 1.05) | 0.177 |
| Esophageal cancer (C15) (n=107) | 0.79 (0.40, 1.54) | 0.480 |
| Colorectal cancer (C18-20) (n=2,621) | 1.02 (0.90, 1.15) | 0.751 |
| GB and biliary tract cancer (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) (m=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 |

HR, hazard ratio; CI, confidence interval

**Figure legend**

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

Figure 1



Cancer Epidemiology, Biomarkers & Prevention

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

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