Prevalence of opioid prescriptions in Taiwan (2008–2018)

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Abstract

Background: Opioids are effective for severe pain; however, the safety issue is also a primary concern. To better understand the opioid use in Taiwan, we conducted this study.

Methods: Data on patients with opioid prescriptions, including morphine, fentanyl, pethidine, codeine, oxycodone, hydromorphone, and buprenorphine were collected using the Taiwan National Health Insurance Database (NHID).

Results: Our analysis of opioid prescriptions from 2008 to 2018 in Taiwan indicated that (1) A slow increase in prevalence of opioid prescription was found during the study period. Among the drugs studied, morphine accounted for the majority of the prescriptions written, with a gradual increase annually. Pethidine prescriptions showed a significant and rapid decline over the years; (2) medical centers prescribed the largest number of opioids, followed by regional hospitals, local hospitals, and clinics; (3) the number of prescriptions per year per capita in cancer group was much higher than that in noncancer group. In noncancer group, most of the prescriptions were used in acute pain service (98.7%); and (4) use of opioids increased with age in both cancer and noncancer patients.

Conclusion: The total number of opioid prescriptions in Taiwan gradually increased annually, among which morphine was the most commonly used opioid. Cancer patients consumed more opioid prescriptions than noncancer patients and most of the prescriptions in noncancer patients were used in acute pain service. The number of prescriptions increased with the age of the patients in both cancer and noncancer patients. The low prescription rate of opioids in chronic pain in Taiwan is not similar as those in high opioid–consuming countries, such as United States.

Keywords: Pain; Prescription; Taiwan

1. INTRODUCTION

In the field of pain treatment, opioids are considered the most effective analgesics. Opioids have been widely used to treat moderate and severe pain. Although opioids relieve pain, the safety issue is also a primary concern.[1–4] According to the World Health Organization's (WHO's) 2020 report,[5,6] opioids were widely used in Europe and the United States of America. The top five countries with average opioid consumption per capita from 2015 to 2017 are United States of America, Germany, Canada, Austria, and Belgium. Dividing the world into six continents,[5,6] North America ranks the most-consumed continent, followed by Oceania, Europe, South America, Asia, and Africa. In the past ten years, there has been a widespread use of opioids in the United States of America, especially from 2015 to 2017,

leading to the opioid epidemic (also known as opioid crisis).[7–9] Therefore, in recent years, countries around the world have increasingly monitored the prevalence of opioid prescription for the safety of their citizens.[10–14] Taiwan is known for its quality health care services, but the prevalence of opioid prescription has been rarely studied and reported. The aim of the study was to investigate the prevalence of opioid prescriptions in Taiwan. In the study, we evaluated the trend of opioid prescriptions during the years 2008 to 2018. We also evaluated the prevalence of opioid prescription in different hospital levels, in cancer and noncancer patients, and in different age groups.

2. METHODS

This population-based study used the Taiwan NHI Research Database (NHIRD) and TCR from the Health and Welfare Data Science Center of the Ministry of Health and Welfare to gather data from 2008 and 2018. The information included all claims of the prescription, treatment types, and medication order from outpatient, emergency, and inpatient on the entire population.

Patients with the records of using opioid prescriptions (morphine, fentanyl, pethidine, codeine, oxycodone, hydromorphone, and buprenorphine) were selected as study population. To understand relevant disease diagnosis among patients using opioid prescriptions, claims of all inpatient and outpatient were used from the National Health Insurance (NHI) reimbursement

datasets, with cancer patients being stratified for analysis. Diseases were defined based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) or *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM). In addition, Taiwan Cancer Registry (TCR) was used to identify the cancer patients, and the cancer types were divided using the *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3).

Since the NHIRD was created based on insurance claims in which surgical anesthesia claims are reimbursed as a package for the entire surgery, the data used in surgical procedure were not collected into the NHIRD. Therefore, in the study, we did not evaluate opioid prescriptions during surgical procedures. Methadone was excluded because it is mostly used for drug addiction treatment, not for pain management, in Taiwan.

To investigate opioid prescriptions at different hospital levels, health facilities were categorized into four levels: medical center, regional hospital, local hospital, and clinic based on hospital accreditation dataset. The prescription data were adjusted for the number of beds per hospital level (the number of prescriptions/the number of beds). Patients with opioid prescriptions were divided into cancer and noncancer groups to retrieve the top five diseases with the largest total number of prescriptions in the eleven-year period for analysis and comparison. In addition, we also analyzed the differences in prescriptions between cancer and noncancer patients as follows: (1) the number of prescriptions per year per capita, (2) the percentage of acute/chronic use per year (a consecutive 3-month prescription of opioids was defined as chronic use), (3) the percentage of intravenous/oral use per year. Otherwise, the prescriptions for cancer and noncancer patients were also divided into five age cohorts (≤12, 13–18, 19–50, 51–64, and ≥65 years old). The rate of opioid prescription per 100 000 population was determined and standardized by dividing the annual number of prescriptions in each age group by year-end population in each age group. We compared the differences among the five age groups in total population, and in cancer and noncancer population.

Linear regression analysis was performed to estimate the trend difference in each opioid prescription from 2008 to 2018. One-way ANOVA with Scheffe posthoc test was used to calculate the differences in annual prescription numbers among groups in the following categories: different hospital levels, the top five cancer and noncancer diseases, and different age groups. The linear trend test was used to evaluate the differences between cancer and noncancer groups in the number of prescriptions per year per capita, and the Pearson χ^2 test used to calculate the differences between cancer and noncancer patients in the percentage of acute / chronic use per year, and the percentage of intravenous/oral use per year. A p value <0.05 was considered significant.

3. RESULTS

As shown in Fig. 1, a total of 1.6 to 1.9 million opioid prescriptions each year for pain management was found in Taiwan from 2008 to 2018, with an upward trend with each consecutive year. Among them, morphine prescriptions were the highest, with a gradually increasing trend over the years. Pethidine, ranking top on the list, had a rapid decline in prescriptions over the years, from around 700 000 prescriptions in 2008 to around 260 000 in 2018. Fentanyl prescriptions have gradually increased from about 210 000 prescriptions in 2008 to ≈400 000 in 2018. Codeine use rose slowly, from about 200 000 prescriptions in 2008 to about 240 000 in 2018; buprenorphine prescriptions have been low (<20 000 prescriptions) over the years with no significant increase. Though
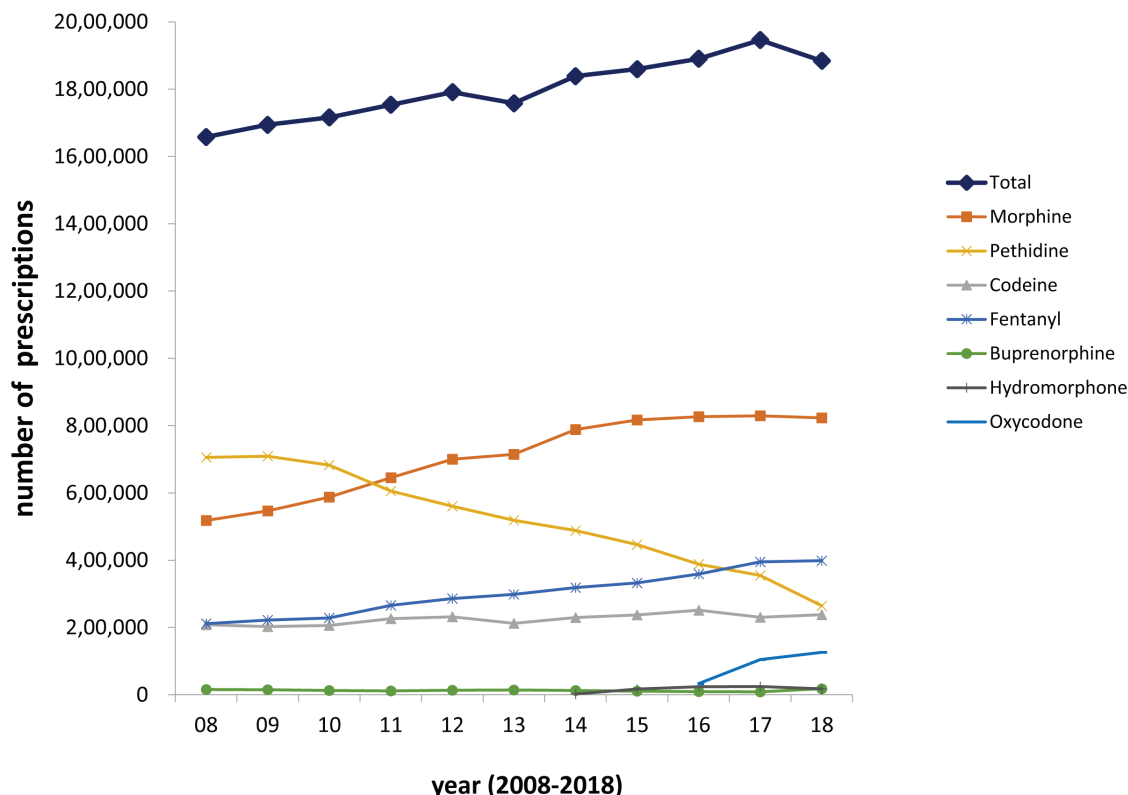

Fig. 1 The trend of opioid prescriptions from 2008 to 2018. Trend test: total, $p < 0.0001$; morphine, $p < 0.0001$; pethidine, $p < 0.0001$; fentanyl, $p < 0.0001$; codeine, $p = 0.0027$; buprenorphine, $p = 0.4159$; hydromorphone, $p = 0.2260$; oxycodone, $p = 0.0203$.

oxycodone was introduced to Taiwan relatively recently in 2015, the number of prescriptions increased from >30 000 in 2016 to >130 000 in 2018. Ever since hydromorphone was introduced to Taiwan in 2014, the number of prescriptions has been steady at around 20 000 from 2014 to 2018, with no significant changes.

After adjusting for the number of beds per hospital level (Fig. 2), the medical center had the highest opioid prescriptions, followed by regional hospital, local hospital, and clinic. The number of prescriptions in the clinic was extremely low. When dividing the patients with opioid prescriptions into cancer and noncancer patients, cancer patients consumed more prescriptions (per year per capita) than noncancer patients (Fig. 3). The percentage of acute / chronic use per year in cancer and noncancer patients were 77.18% / 22.82% vs 98.7% / 1.30% (mean), respectively ($p < 0.0001$), and the percentage of intravenous / oral use per year in cancer and noncancer patients were 44.01% / 55.99% vs 88.16% / 11.84% (mean), respectively ($p < 0.0001$). Cancer patients (Fig. 4A) who received the highest amount of prescription opioids in eleven-year period were patients with lung/bronchial cancer, colorectal cancer, liver/bile duct cancer, oral cancer, and female breast cancer. noncancer patients (Fig. 4B) receiving the highest amount of opioids were those with kidney/ureteral stones, gallbladder stones, abdominal pain, knee arthritis, and hip fractures. Comparing opioid use in different age groups, the number of opioid prescriptions increased with age (Fig. 5A), even when the patients were divided into cancer (Fig. 5B) and noncancer (Fig. 5C) groups. When analyzing differences among age groups, only cancer patients aged ≦12 years and between 13 and 18 revealed no significant difference.

4. DISCUSSION

There are several important findings in the study: (1) during 2008 to 2018, opioid prescriptions in Taiwan had maintained a steady pace with slight increases (<20%). Among them, morphine was still at the top of the most frequently prescribed opioids while pethidine prescriptions had a significant downward trend over the years. (2) Health facilities that issued the largest number of opioid prescriptions by hospital levels, in the order of highest to least, are medical center, regional hospital, local hospital, and clinic. (3) Cancer patients consumed more opioid prescriptions than noncancer patients and most of the prescriptions in noncancer patients were used in acute pain service. (4) Opioid prescriptions increased with age in both cancer and noncancer patients.

According to the WHO's 2020 report,[5,6] there was markedly increase in opioid consumption (>100%) in countries that used large quantities of opioids (such as in North America and some European countries) over the past ten-year period. Our study shows that the total opioid prescriptions in Taiwan have increased gradually in small amplitude in the past decade, with the most frequently prescribed opioid being morphine. Fentanyl ranked second, according to the 2018 report in Taiwan. In the United States, hydrocodone, oxycodone, and fentanyl are widely utilized,[5–9] whereas oxycodone, fentanyl, and hydromorphone are more commonly used in other countries with high opioid consumption.[5,14,15] Oxycodone was introduced in Taiwan in 2015. Although the number of prescriptions increased during 2015 to 2018, the total number was low. In addition, the number of hydromorphone prescriptions has been low, most likely due to only long-acting dosage form of the drug being available in Taiwan, which makes it inconvenient to use. Around the
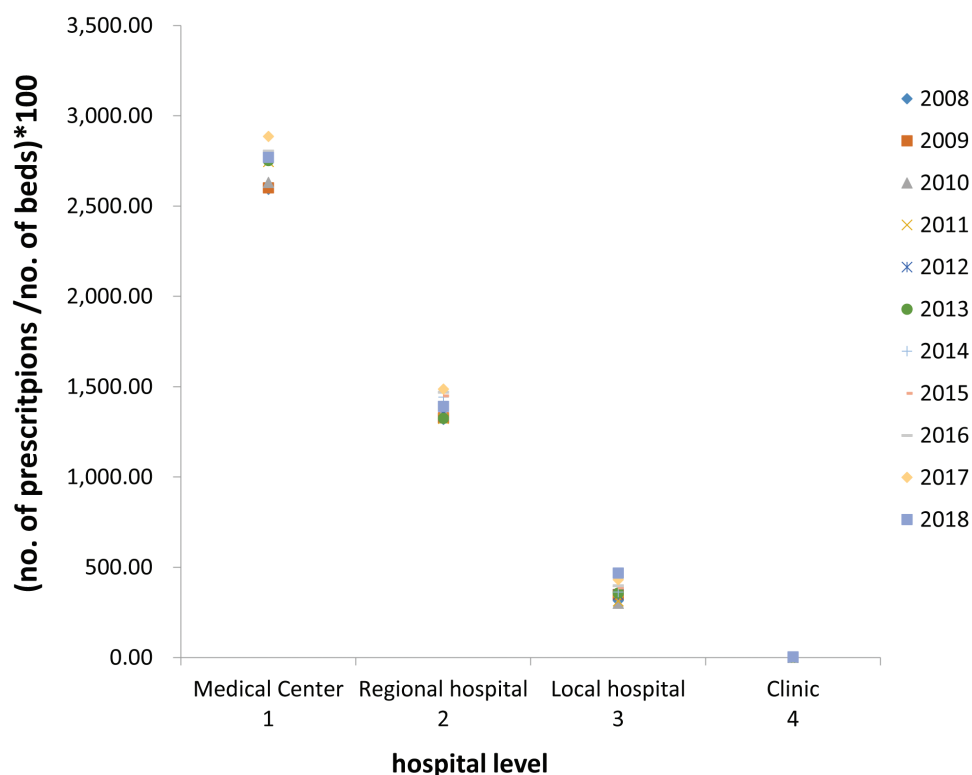

Fig. 2 Prevalence of opioid prescriptions in different hospital levels. One-way analysis of variance ($p < 0.0001$). The Scheffe post hoc test: 2 vs 1 $p < 0.05$; 3 vs 2 $p < 0.05$; 4 vs 3 $p < 0.05$; 3 vs 1 $p < 0.05$; 4 vs 1 $p < 0.05$; 4 vs 2 $p < 0.05$.
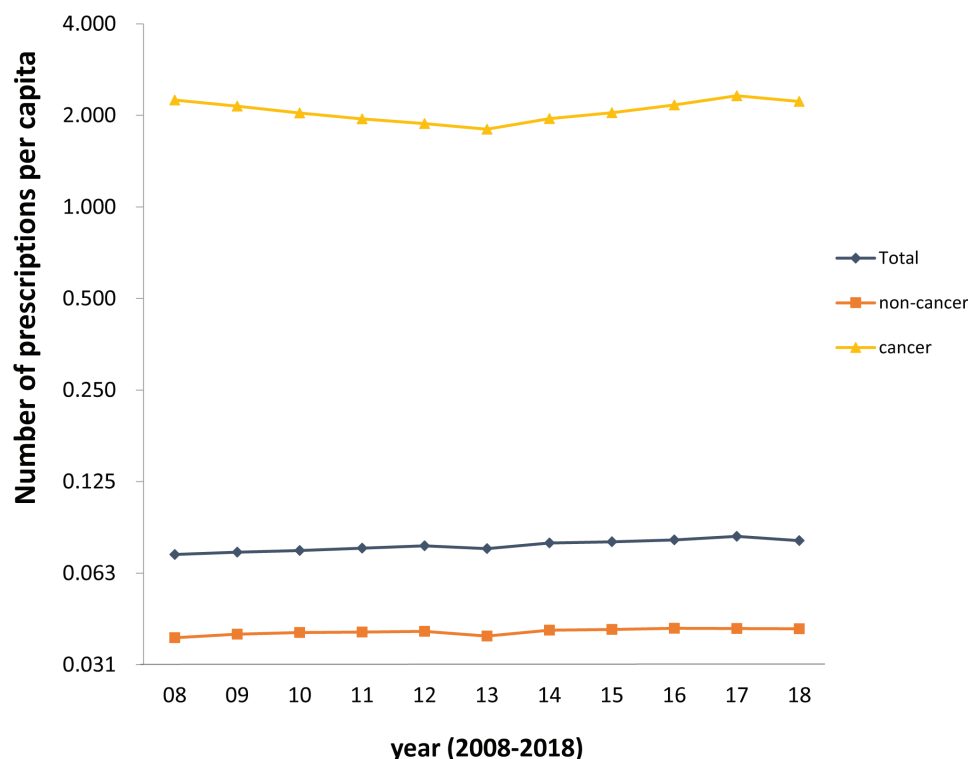
Fig. 3 Number of opioid prescriptions per capita between cancer and noncancer patients. The difference between cancer patients and noncancer patients was significant ($p < 0.0001$, by linear trend test).

world, physicians' choice of drugs is often affected by several factors,[11,13,16,17] such as awareness and attitude of the health care professionals and public toward the use of opioids, promotion of pharmaceutical companies, support of the medical associations, government policies on drug distribution and control, and hospital accreditation system.

The study results also revealed that the number of pethidine prescriptions has declined sharply over the decade since 2008 owing to effective drug education and relevant comprehensive regulations in Taiwan.[18,19] Since prolonged use of pethidine may lead to 6-norpethidine accumulation and cause central nervous side effects such as seizure,[20,21] there is an international consensus to reduce pethidine prescribing and replace it with other opioids.[20,21] Taiwan also aligns with this global trend. Buprenorphine is a partial agonist at the mu-receptor and can cause antagonism when mixed with other opioids; thus, it is not commonly used for pain management in Taiwan.[22,23]

The study also found that the number of opioid prescriptions issued by medical centers is higher than that in other levels of health facilities, followed by regional hospitals, local hospitals, and clinics. This made Taiwan different from some of other countries where opioids were mostly prescribed by clinic physicians.[10,15,17,24] This difference may be attributed to differences in healthcare models.

We found the patients in noncancer group consumed less opioid prescriptions than those in cancer group, and most of the prescriptions were used in acute pain service. These findings were quite different from those reported in high opioid consuming countries, such as in United States of America, Canada, and United Kingdom, etc. In those countries, most of the opioid prescriptions were used in noncancer chronic pain.[9–16] The low prescription rate is common seen in Asian countries and may be due to differences in Eastern and Western cultures and concerns about the use of opioids.[13,25–29]

According to our study results, for cancer patients treated with opioids for pain, lung/bronchial cancer patients were the most frequent users, followed by patients with colorectal, cancer, liver/bile duct cancer, oral cancer, and female breast cancers. After integrating the findings into the Data on Cause of Death in Taiwan from 2008 to 2018, the above cancers are also align with the leading causes of cancer death in Taiwan. The top five causes of cancer death in order and the percentage of times the previously mentioned cancers appearing on the list were lung/bronchial cancer (100%), liver/bile duct cancer (100%), colorectal cancer (100%), female breast cancer (100%), and oral cancer (82%). For patients with noncancer pain, those with kidney or ureteral stones are most commonly prescribed opioids, followed by abdominal pain, biliary stones, knee arthritis, and hip fractures, mostly for acute pain and some for chronic pain. Our study also found that the number of opioid prescriptions for both cancer and noncancer patients increased with age. The increased opioid use with age can be explained by an increase in pain-related discomfort with age regardless of cancer status.

There are limitations to this study: (1) opioid prescriptions in surgery were not included in the study since they are not collected in the Taiwan NHIRD. (2) Dosage per prescription was not analyzed in the study because it requires more detailed data and is worth further exploration. (3) An analysis of opioid use for each disease was not performed; it is worth further study.

In conclusion, according to our study, the total number of opioid prescriptions in Taiwan has risen gradually from 2008 to 2018, among which morphine was the most commonly used opioid. Medical center wrote the largest number of opioid prescriptions, followed by regional hospital, local hospital, and clinics. Cancer patients consumed more opioid prescriptions than noncancer patients and most of the prescriptions in noncancer patients were used in acute pain service. For cancer patients, opioids were most commonly
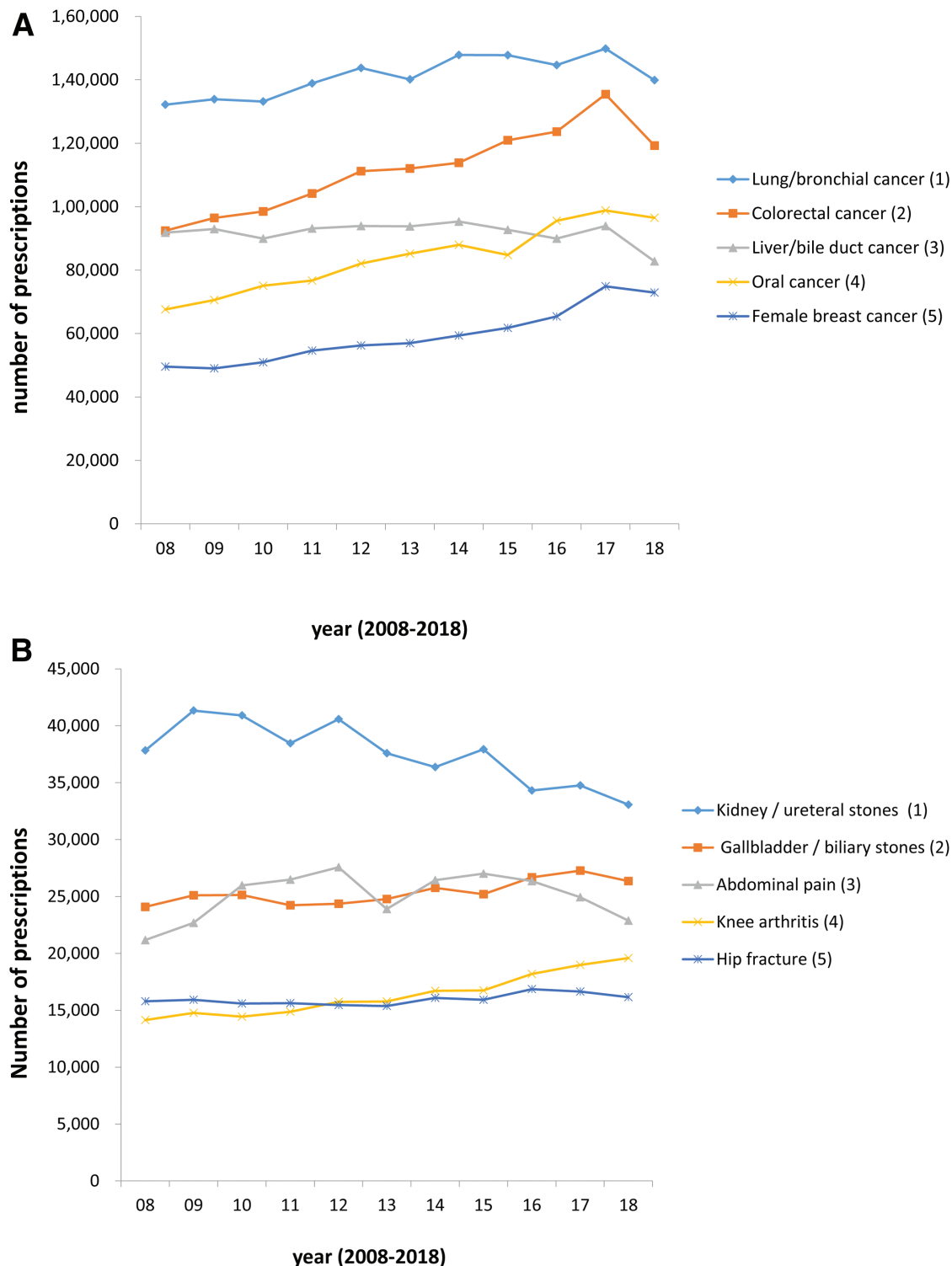
Fig. 4 Prevalence of opioid prescriptions. A, In cancer patients. One-way analysis of variance ($p < 0.0001$). The Scheffe post hoc test: 2 vs 1 $p < 0.05$; 3 vs 2 $p < 0.05$; 4 vs 3 n.s.; 5 vs 4 $p < 0.05$; 3 vs 1 $p < 0.05$; 4 vs 1 $p < 0.05$; 5 vs 1 $p < 0.05$; 4 vs 2 $p < 0.05$; 5 vs 2 $p < 0.05$; 5 vs 3 $p < 0.05$. B, In noncancer patients. One-way analysis of variance ($p < 0.0001$). The Scheffe post hoc test: 2 vs 1 $p < 0.05$; 3 vs 2 n.s.; 4 vs 3 $p < 0.05$;5 vs 4 n.s.; 3 vs 1 $p < 0.05$; 4 vs 1 $p < 0.05$; 5 vs 1 $p < 0.05$; 4 vs 2 $p < 0.05$; 5 vs 2 $p < 0.05$; 5 vs 3 $p < 0.05$. n.s. = not significant.

prescribed for pain in lung/bronchial cancer, colorectal cancer, liver/bile duct cancer, oral cancer, and female breast cancer. For noncancer patients, opioids were mainly prescribed for kidney/ureteral stones, gallbladder/biliary stores, abdominal pain, knee arthritis, and hip fractures. The number of opioid prescriptions increases with the age of patients (cancer or non-cancer). The study results can provide insight for the international medical community.
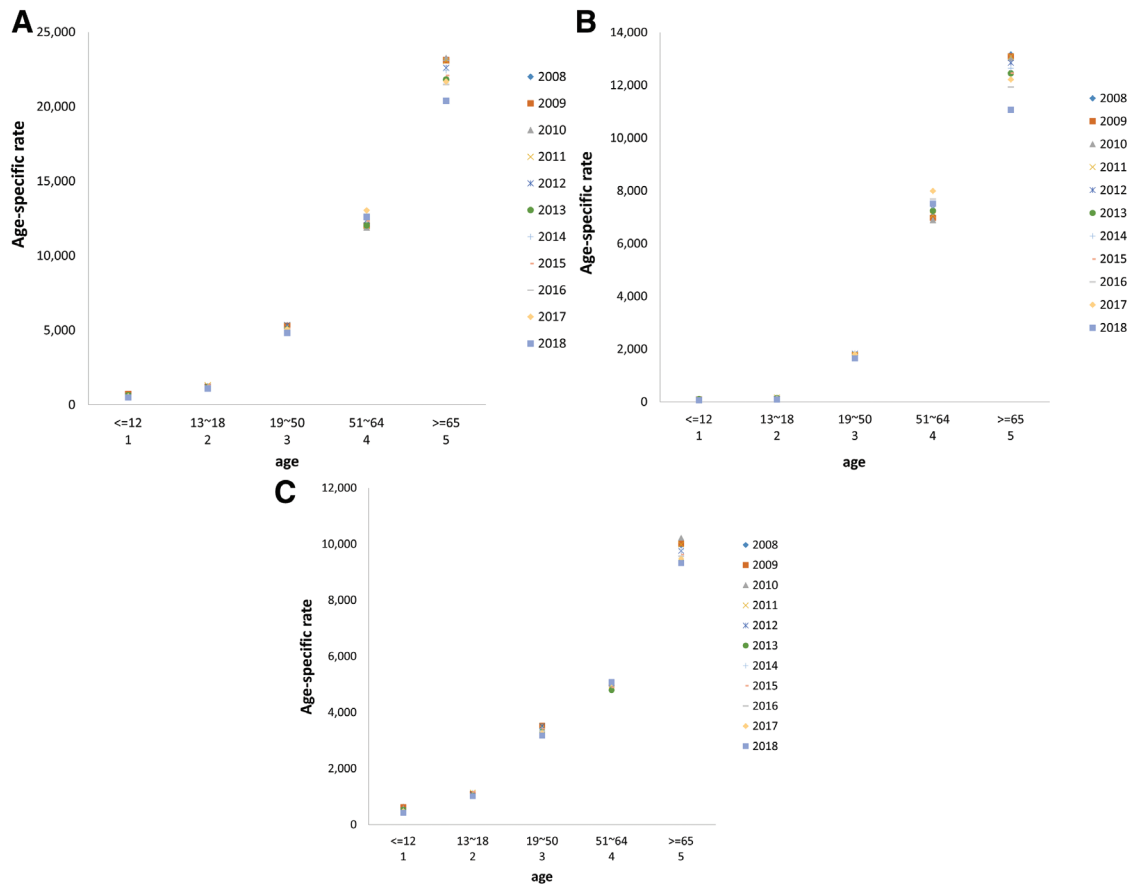
Fig. 5 Prevalence of opioid prescriptions. A, In different age groups. One-way analysis of variance ($p < 0.0001$). The Scheffe post hoc test: 2 vs 1 $p < 0.05$; 3 vs 2 $p < 0.05$; 4 vs 3 $p < 0.05$; 5 vs 4 $p < 0.05$; 3 vs 1 $p < 0.05$; 4 vs 1 $p < 0.05$; 5 vs 1 $p < 0.05$; 4 vs 2 $p < 0.05$; 5 vs 2 $p < 0.05$; 5 vs 3 $p < 0.05$. B, In cancer patients in different age groups. One-way analysis of variance ($p < 0.0001$). The Scheffe post hoc test: 2 vs 1 n.s.; 3 vs 2 $p < 0.05$; 4 vs 3 $p < 0.05$; 5 vs 4 $p < 0.05$; 3 vs 1 $p < 0.05$; 4 vs 1 $p < 0.05$; 5 vs 1 $p < 0.05$; 4 vs 2 $p < 0.05$; 5 vs 2 $p < 0.05$; 5 vs 3 $p < 0.05$. C, In noncancer patients in different age groups. One-way analysis of variance ($p < 0.0001$). The Scheffe post hoc test: 2 vs 1 $p < 0.05$; 3 vs 2 $p < 0.05$; 4 vs 3 $p < 0.05$; 5 vs 4 $p < 0.05$; 3 vs 1 $p < 0.05$; 4 vs 1 $p < 0.05$; 0.05; 5 vs 1 $p < 0.05$; 4 vs 2 $p < 0.05$; 5 vs 2 $p < 0.05$; 5 vs 3 $p < 0.05$. n.s. = not significant.

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