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Trends in strong opioid prescription for cancer patients in Japan from 2010 to 2019: An analysis with large medical claims data

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Running title

Opioid trends for cancer patients in Japan

Abstract

Background

Consumption of opioids, essential drugs for pain relief, has seen rapid growth worldwide.

In Japan, where total opioid consumption still remains low among developed countries, little is known about trends in the clinical patterns of opioids in terminally ill cancer patients.

Methods

Patients who died of cancer from 2010 to 2019 were included in this study. Morphine, oxycodone, fentanyl, tapentadol, methadone, and hydromorphone were examined as opioids for cancer pain. We calculated the prevalence of prescribed opioids prior to death by year and age group and the average opioid dose 30 days before death.

Results

The total number of patients was 221,598. We found that the prescription prevalence of opioids increased from 60.8% to 65.9% (5.1%). Morphine was most prescribed in 2010 but had decreased prevalence (-9.0%) during the 10-year period. Oxycodone had the

highest increase in prescription prevalence (13.7%), and fentanyl prevalence decreased (-4.9%). In the subgroup comparison, the prescription prevalence of opioids in the elderly was lower than that in the younger group; however, the increasing trend in the elderly was greater than that in the younger group. The percentage of patients prescribed low-dose opioids (<60 mg/day) during the 30 days before death increased by 4.9% and was the highest throughout the study period.

Conclusion

The prevalence of opioid prescriptions for terminally ill cancer patients has increased from 2010 to 2019 in Japan. The opioid-specific trends were similar to the global trend but differed by palliative care specialty.

mini-abstract

The opioid prescriptions for cancer patients has increased in Japan from 2010 to 2019. The opioid-specific trends were similar to the global trend but differed by palliative care specialty.

Key words

opioids, cancer pain, pain management, palliative care, health claim database

Introduction

Opioids are essential for the relief of cancer pain as well as acute, post-operative, and chronic non-cancer pain, although, opioid use for chronic pain remains controversial (1).

Since the importance of pain relief and palliative care has been internationally recognized, increasing opioid consumption has been reported worldwide over the last 30 years, especially in developed countries (2,3). However, in countries with high opioid consumption, opioids are mostly used for non-cancer-related pain, and the prescribed opioids have become a serious public health problem because of their abuse (4–7).

Several studies have shown that opioid consumption for non-cancer patients was dominant in Germany (75%) and Denmark (78%) (8,9). In Japan, with the total opioid consumption remaining much lower than that in other developed countries, prescriptions for non-cancer chronic pain are more strictly regulated than those for cancer pain.

Oxycodone prescriptions for non-cancer pain have only recently become insured in 2020 and are not yet widely available. In a previous study in Japan, Sato et al. used administrative databases from acute care hospitals to investigate the prevalence of opioid

prescriptions as end-of-life care and found that the prevalence was 47–64% in the 14 days before death (10). Opioid prescribing for terminally ill cancer patients is thought to be approximately the same as the 50% rate in the UK study (11), but the trends in opioid prescriptions among cancer patients in Japan over the past 10 years are unknown. It is important to know the trends of opioid prescribing in Japan, since the policies of Cancer Control Act and the PEACE program education have promoted the use of opioids for cancer patients. Moreover, understanding the clinical use of opioids for cancer pain is important for implementing better cancer pain management and palliative care; however, little has been published in Japan on trends in opioid prescription for cancer patients, including trends by age group and type of opioid.

This study aimed to identify trends in opioid prescription and use for terminally ill cancer patients from 2010 to 2019 in Japan and to explore the factors that explain these trends.

Methods

This study of de-identified patient data is exempt from the Ethical Guidelines for Medical and Biological Research Involving Human Subjects and does not require approval from an institutional review board in Japan.

Data sources

This analysis used inpatient claims data from January 1, 2010, to December 31, 2019, collected by Medical Data Vision, Inc. (MDV). The MDV database is anonymized to protect personal information and contains longitudinal claims data from acute care hospitals that employ the Diagnostic Procedure Combination/Per Diem Payment System (DPC/PDPS). The use of medical claims data is suitable for investigating opioid prescriptions, given that there is no burden on patients or healthcare providers in collecting daily clinical data. There are 5,809 general hospitals in Japan, of which 1,390 hospitals participated in DPC/PDPS in 2010 and 1727 hospitals in 2019. Approximately 70% of cancer patient deaths occur in general hospitals. The DPC data used for payments included patient demographics and clinical information, diagnoses, procedures, medications, and outcomes at discharge. Diagnoses were recorded using International

Classification of Diseases, Tenth Revision (ICD-10) codes. There are six categories of diagnoses in DPC: the main diagnosis, admission-precipitating diagnosis, most resource-consuming diagnosis, second most resource-consuming diagnosis, comorbidities present at the time of admission, and conditions arising after admission.

MDV's current coverage is approximately 22% of the total number of DPC hospitals in Japan (1,727 hospitals as of April 1, 2019).

Patients

Patients registered in the MDV database from 2010 to 2019 who had died of cancer were included in the study after excluding those who were under 20 years of age. Patients were considered to have died of cancer when the ICD-10 code (C00-97) of malignancy neoplasm appeared as 'the main diagnosis' or 'admission-precipitating diagnosis' or as 'most resource-consuming diagnosis' and the outcome of that admission was death, with reference to the methods of the studies by Sato et al. (10) and Yamana et al (12).

Opioid analgesics

We investigated the following strong opioids with insurance claims for cancer pain in Japan: morphine, oxycodone, fentanyl, tapentadol, methadone, and hydromorphone.

Methadone tablets were launched in 2013, tapentadol tablets in 2014, hydromorphone tablets in 2017, and hydromorphone injections in 2018.

Mean Daily Opioid Dose

We calculated the average opioid dose 30 days prior to death. The mean daily opioid dose was defined as the daily average of the oral morphine equivalents (OMEQ) of opioids prescribed within 30 days before death. The Defined Daily Dose (DDD) established by WHO was used for conversion to OMEQ. The DDD is designed for statistical purposes and avoids the problem of various handbooks showing different equality. The DDDs used for the conversions are listed in Table 1. Because the DDD for injectable fentanyl as an analgesic is not defined, the WHO article was used as a reference (13). (e.g. 1 mg of injectable fentanyl being as potent as 100 mg of oral morphine.)

If opioids were first prescribed on the day of death, the OMEQ prescription dose was

divided by 1 day. Opioids prescribed within 5 days of surgery were excluded because of the use of opioids for surgical anesthesia and postoperative pain.

Statistical Analysis

First, descriptive statistics were used to report outcomes, including demographic characteristics and prevalence of prescribed opioids. The opioids used at the time of death were operationally defined as the last opioid prescribed within 2 weeks prior to death. If the date of the last prescription was more than 2 weeks before the date of death, opioids were considered not to be used at the time of death, because it is not common for acute care hospitals in Japan to prescribe more than a 2-week supply of opioids to patients during hospitalization.

Second, the prescribed opioid prevalence trends from 2010 to 2019 were described in the analysis. Overall, hospital size-specific and age group trends were examined. Larger hospitals and palliative care wards in Japan have more specialized staff and teams for palliative care. Therefore, we calculated the prevalence of opioid prescriptions divided into hospitals with less than 199 beds, 200–499 beds, more than 500

beds, and palliative care wards. Age was stratified into eight groups based upon the date of death (i.e., 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89 and ≥ 90 years old), and the prevalence of opioid prescriptions was calculated by age group. Weighted least square regression was used to examine the trends and their 95% confidence intervals (CI) of annual change in the prescription prevalence. In the regression, the annual prescription prevalence was an outcome and year was a predictor, and the population size of each year was set as a weight.

All analyses were performed with SAS 9.2 software (SAS Institute, Cary, NC, USA).

Results

Table 2 shows the characteristics of the study participants. The total number of participants who died of cancer in our study was 221,598. The mean age at death was 73.3 years (standard deviation [SD], 11.7 years), and two-thirds of participants were male (60.9%). Proportions of primary sites of malignancy that were frequently shown in our study participants were as follows: lung (19.1%), colorectal (10.7%), stomach (11.3%), pancreas (10.4%).

Figure 1 and Table 3 show the trends in prescription prevalence for predominant opioids from 2010 to 2019 and the slope from the regression analysis. Total opioid prescription prevalence among cancer patients before death in Japan significantly increased by 5.1% (60.8% in 2010 to 65.9% in 2019, slope, 0.733; 95% CI, 0.731 to 0.735). The most frequently used opioid analgesic was morphine, and a 9% decrease was observed in the 10-year period (36.1% in 2010 and 27.1% in 2019; slope: -0.959; 95% CI: -0.961 to -0.958). Oxycodone had the highest increase (13.7%) in prescription prevalence, from 4.7% in 2010 to 18.4% in 2019, surpassing fentanyl as the second most

frequently used strong opioid analgesic in 2017. Fentanyl decreased slightly throughout the study period (-4.9%). Hydromorphone, a drug launched in 2017, seems to have replaced other opioids. Tapentadol and methadone have almost never been used in Japan, accounting for 0.08% and 0.05% of the total, respectively, over the study's 10-year period.

Figure 2 shows the hospital size-specific trends in opioid prescription prevalence. The average prevalence of overall opioid use was high in the large-sized hospitals (Figure 2c) and palliative care wards (Figure 2d). This between-hospital gap shrunk over the 10-year period. In small hospitals with 199 or fewer beds, fentanyl was most frequently prescribed for cancer patients compared with morphine since 2015, while in palliative care wards and hospitals with more beds, morphine was most frequently prescribed throughout the study period. In medium-sized hospitals with 200–499 beds, fentanyl was used second to morphine during the study period. In larger hospitals with more than 500 beds, the prevalence of oxycodone increased compared with fentanyl after 2016, and this gap widened in palliative care wards. The use of hydromorphone in palliative care wards in 2019 was 9.8%, with an increase of 9.7% over the 3 years since its launch in year 2017,

and the increase was greater in hospitals with larger bed sizes and in palliative care wards.

Figure 3 shows the trends in opioid prescription prevalence according to age group. More patients in the 30–39, 40–49, and 50–59 age groups received opioids than those in the elderly groups (Fig 3). However, for each elderly group over 70 years of age, the regression slopes ranged from 1.026 to 1.261, indicating an increase in prescription prevalence between 2010 and 2019 (Table 3). The prescription prevalence in the 20–29 year olds may have been unstable due to the small number of patients.

There was a higher proportion of patients in the low dose (< 60 mg/day) group of the four dose ranks of mean OMEQ per patient in the 30 days before death (Fig. 4). Changes included an increase in the percentage of people who used low doses (<60 mg/day) by +4.9%. There were no major changes in the other dose groups, although there was a slight increase in the relatively low-dose group (≥ 60 mg/day and < 120 mg/day) (Fig. 4).

Discussion

This is the first study to clarify the trend in opioid prescribing for terminally ill cancer patients in Japan from 2010 to 2019. We found that the prescription prevalence of opioids increased slightly from 60.8% to 65.9% during the study period. These results are similar to those of previous studies that examined opioid use prevalence among terminally ill cancer patients (10,11). In the United States of America, where opioid consumption is dramatically increasing, the abuse of prescribed opioids has become a serious public health problem, and the regulations have become more severe in recent years. As a result, opioid consumption declined, as did prescriptions for terminally ill cancer patients (14).

In Japan, opioid prescriptions for cancer patients are increasing, although opioid consumption is believed to have remained low. The opioid consumption disclosed by the International Narcotics Control Board (INCB) includes use not only for cancer patients but also for anesthesia, non-cancer, and even abuse. This study showed that the prevalence of opioid prescriptions for cancer patients in Japan is not low compared with that in other developed countries. This may imply that the use of opioids for cancer patients are

promoted with a successful balance between opioid regulation and medical use in Japan.

Morphine has always been the most commonly used strong opioid for cancer patients before death; however, the prescription prevalence of morphine has been declining. The

highest increase in use (13.7%) was observed for oxycodone. This trend was common, with morphine on the decline and oxycodone on the rise in other developed countries (15).

The prevalence of cancer patients who received fentanyl decreased throughout the study period (-4.9%), whereas fentanyl consumption in Japan, as published by the INCB, has

increased significantly compared to other opioids (16). This result suggests that the increase in fentanyl consumption can be attributed to its use in surgery and acute care,

because fentanyl is still not widely prescribed for non-cancer pain, although fentanyl transdermal is covered by insurance, due to the caution required by the guidelines of the

Japanese Society of Pain Clinicians. Trends in opioid prescribing from 2010 to 2019 showed a decrease in morphine and fentanyl and an increase in oxycodone. This trend is

considered to be influenced by the launch of oxycodone injection in 2012, which provided an option for patients who could not take internally, where previously only morphine

injection and fentanyl patches were available. Methadone, used mainly in the treatment of addiction in other countries, was almost never prescribed. This is possibly because the available form in Japan is limited to tablets and there are special licenses and criteria for prescribing methadone.

In small-and medium-sized hospitals, morphine, the most experienced injectable opioid, and transdermal fentanyl, which is easy to use, were the two main opioids prescribed before death when oral intake becomes difficult. Oxycodone, which has a relatively new injectable form, and hydromorphone, which launched in 2017, had increased prescription prevalence, especially in hospitals that have more specialized palliative care staff. Education and professional staffing may change future trends, because relatively new opioids are more frequently used in hospitals with more palliative care specialists, while traditionally used and easier to use opioids are more frequently used in hospitals with fewer specialists. Depending on the size of the hospital, meaning the specialty of the palliative care team, the types of opioids commonly used were different. Education and professional development are critical if the use of new opioids

leads to more appropriate pain management and care for cancer patients.

In terms of age groups, prescription prevalence was higher in the 30–39, 40–49, and 50–59 age groups than in the ≥ 70 years groups. Many previous studies have reported a decrease in opioid use among the elderly (11,16–18). Among developed countries, Japan is facing a super-aging society, and cancer patients are also getting older. Considering the aging population, the overall use of opioids for cancer patients might be higher than that in other countries. While the overall prevalence of opioid prescriptions among the elderly is low, it has shown an increasing trend from 2010 to 2019. Although elderly patients are considered to have less pain, the untreated population and the increased access to opioids in this population may have contributed to the trend of increased the prevalence. This positive change may be attributed to the policy of Cancer Control Act and PEACE program education. Cancer Control Act placed importance on palliative care for cancer patients and their families, and palliative care systems were to be developed. One of its policies is the PEACE program, a two-day educational course intended to be covered by all physicians engaged in cancer care, which promote the use of opioids in the treatment

of cancer pain.

The highest proportion of patients was prescribed low opioid doses (mean OMEQ<60 mg). A previous United Kingdom study reported that annual mean OMEQ had the highest proportion of ranks with low doses (≤ 50 mg) at 40%(1). Although there is a difference between the average of the 30 days before death in this study and the average of 1 year in the UK study, it does not seem to be substantially different. In Japan, the total increase in prevalence for the two opioid dose groups (<60 mg and 60–120 mg) approximately matched the increases for all opioids. The high-dose opioid use group had a certain percentage of patients in each year, but there was no significant trend change.

There has been a slight increase in the use of opioids for terminally ill cancer patients from 2010 to 2019, suggesting that this change has led to the prescription of low-dose opioids in elderly patients with inadequate pain treatment. Considering that the percentage of elderly cancer patients who are likely to receive less or no opioids is increasing as a result of the aging of society, this may be one of the reasons why overall opioid consumption has not increased in Japan, despite the increasing prevalence of

opioid prescriptions for cancer patients.

This study had several limitations. First, the insurance claims data used in this study were from DPC hospitals, which are acute care hospitals and may not necessarily reflect the actual status of opioid prescriptions among cancer patients before death in Japan as a whole. Only opioids that were in use at the time of death were analyzed; not all opioids that cancer patients used during their illness. In addition, only strong opioids were examined in this study, which may underestimate the opioid use of tramadol and codeine, which are weak opioids that can be easily prescribed by clinicians in Japan without special licenses. However, the opioids used at the time of death were investigated, and since in Japan injectable tramadol is insured for intramuscular injection and codeine is only available in tablet form, it is unlikely to have a significant impact. Second, we need to examine the validity of the diagnoses and drugs, because we used insurance claims data. Nonetheless, insurance claims data is considered to be reliable regarding malignancy, because Yamana et al. reported that the validity of diagnosis in Japanese DPC data was 83.5% for sensitivity, 97.7% for specificity, 94.2% for positive predictive value,

and 93.0% for negative predictive value for malignancy (12). Third, the data collected by the MDVs used in this study showed that the number of DPC hospitals participating in the MDVs increased during the study period; therefore, the number of cancer deaths increased accordingly. Relatively active DPC hospitals participated in the initial period of the study, and the quality of the hospitals covered each year may have been heterogeneous throughout the study period.

In conclusion, the prescription prevalence of opioids for terminally ill cancer patients has increased in Japan from 2010 to 2019. It is true that, as in other countries, access to opioids for cancer patients needs to be more improved, especially the elderly. The opioid-specific trends were similar to the global trend but differed by palliative care specialty. The education of palliative care specialty may be the key to future opioid trends in Japan. Further, it is necessary to study the clinical use of opioids not only in DPC hospitals but also in non-acute hospitals, so that cancer patients in Japan can equally receive opioid therapy anywhere.

Disclosures and Acknowledgments

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The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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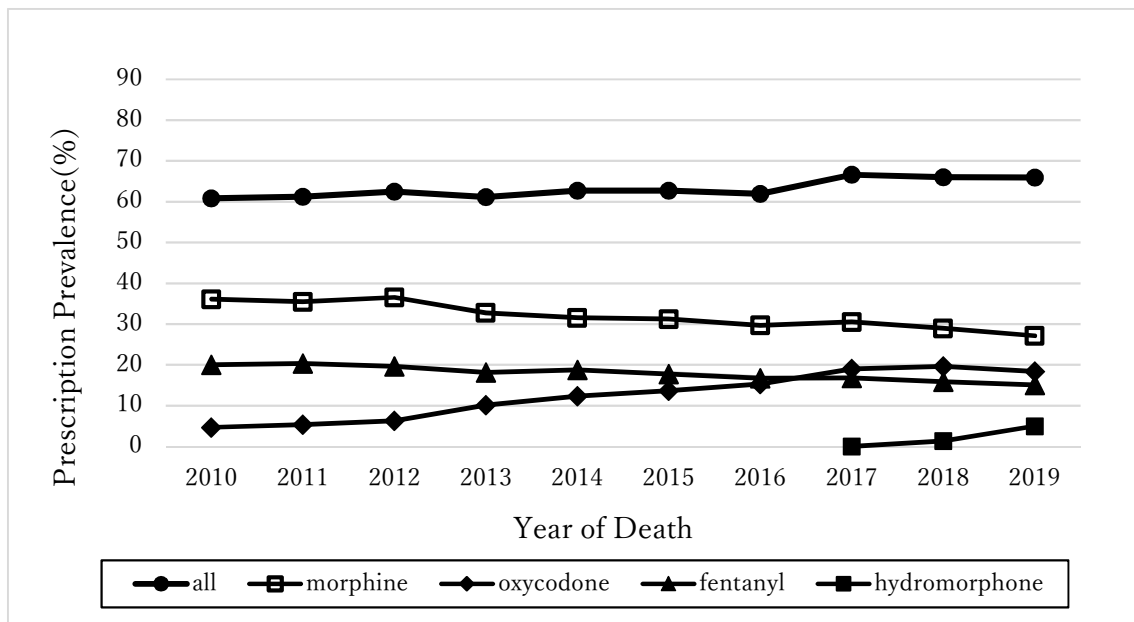


Fig 1. Prescription prevalence (%) of opioids for patients with cancer before death, 2010 to 2019

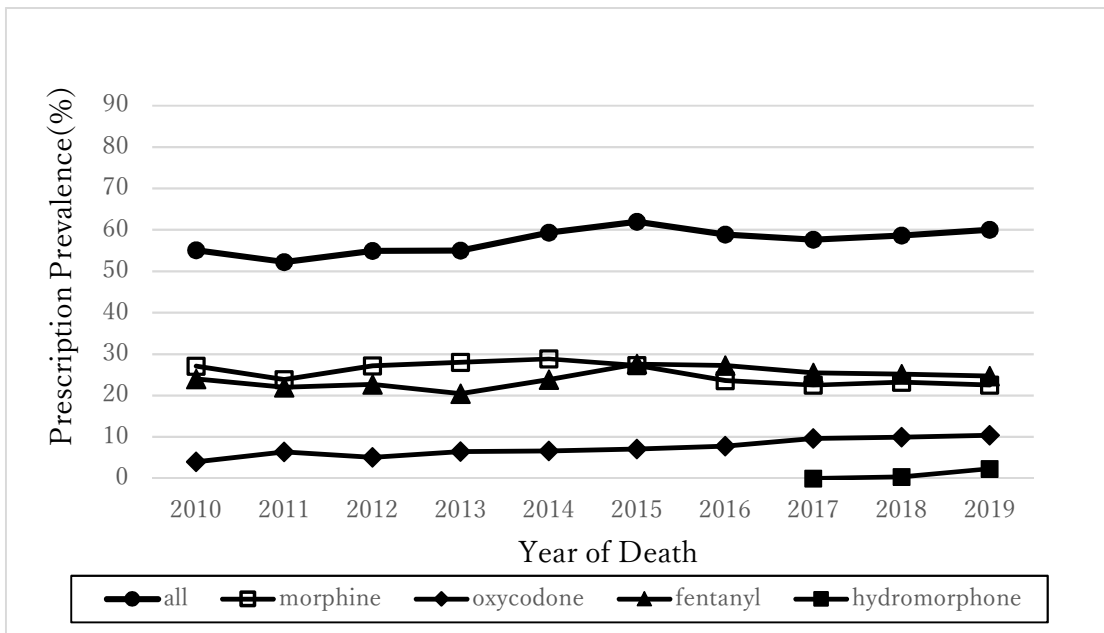


Fig 2. (a)

Prescription prevalence (%) of opioids for patients with cancer before death, 2010 to 2019.

(a) Small hospitals (≤ 199 beds), (b) Medium-sized hospitals (200 to 499 beds), (c) Large hospitals (≥ 500 beds), (d) Palliative care wards

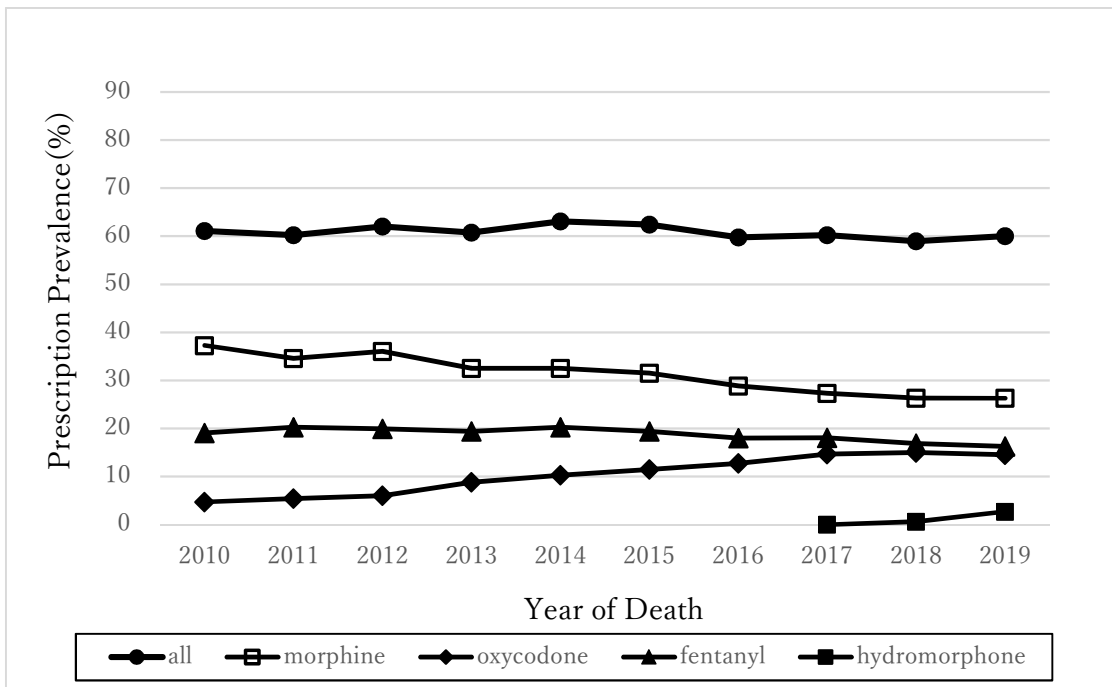


Fig 2. (b)

Prescription prevalence (%) of opioids for patients with cancer before death, 2010 to 2019.

(a) Small hospitals (≤ 199 beds), (b) Medium-sized hospitals (200 to 499 beds), (c) Large hospitals (≥ 500 beds), (d) Palliative care wards

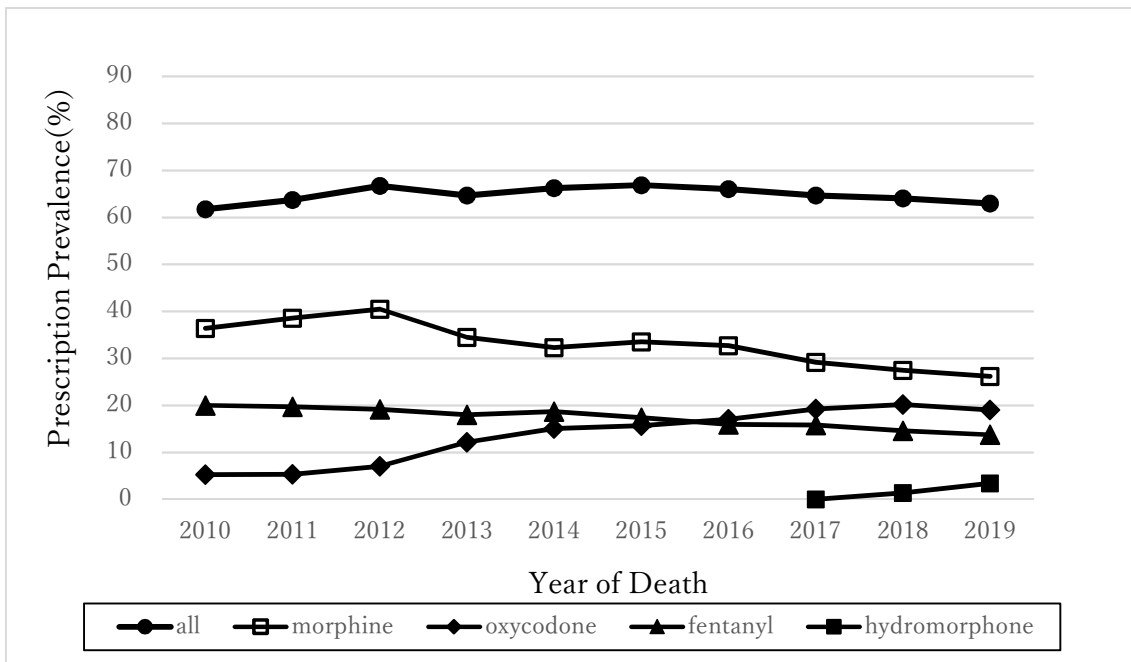


Fig 2. (c)

Prescription prevalence (%) of opioids for patients with cancer before death, 2010 to 2019.

(a) Small hospitals (≤ 199 beds), (b) Medium-sized hospitals (200 to 499 beds), (c) Large hospitals (≥ 500 beds), (d) Palliative care wards

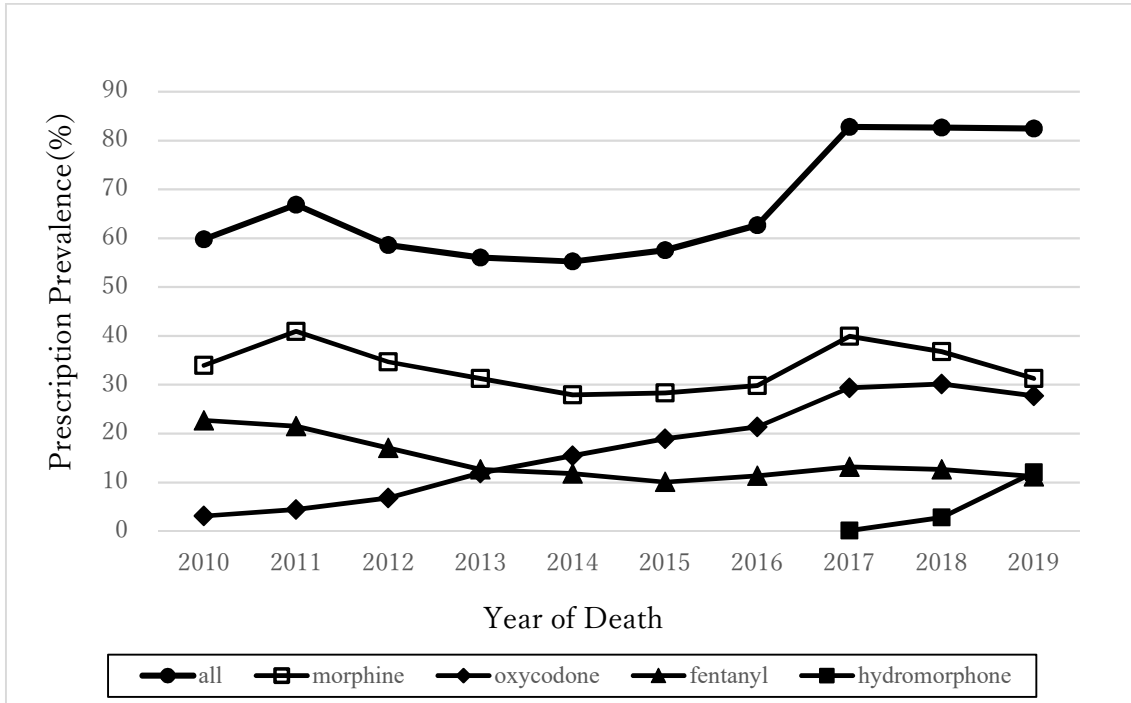


Fig 2. (d)

Prescription prevalence (%) of opioids for patients with cancer before death, 2010 to 2019.

(a) Small hospitals (≤ 199 beds), (b) Medium-sized hospitals (200 to 499 beds), (c) Large hospitals (≥ 500 beds), (d) Palliative care wards

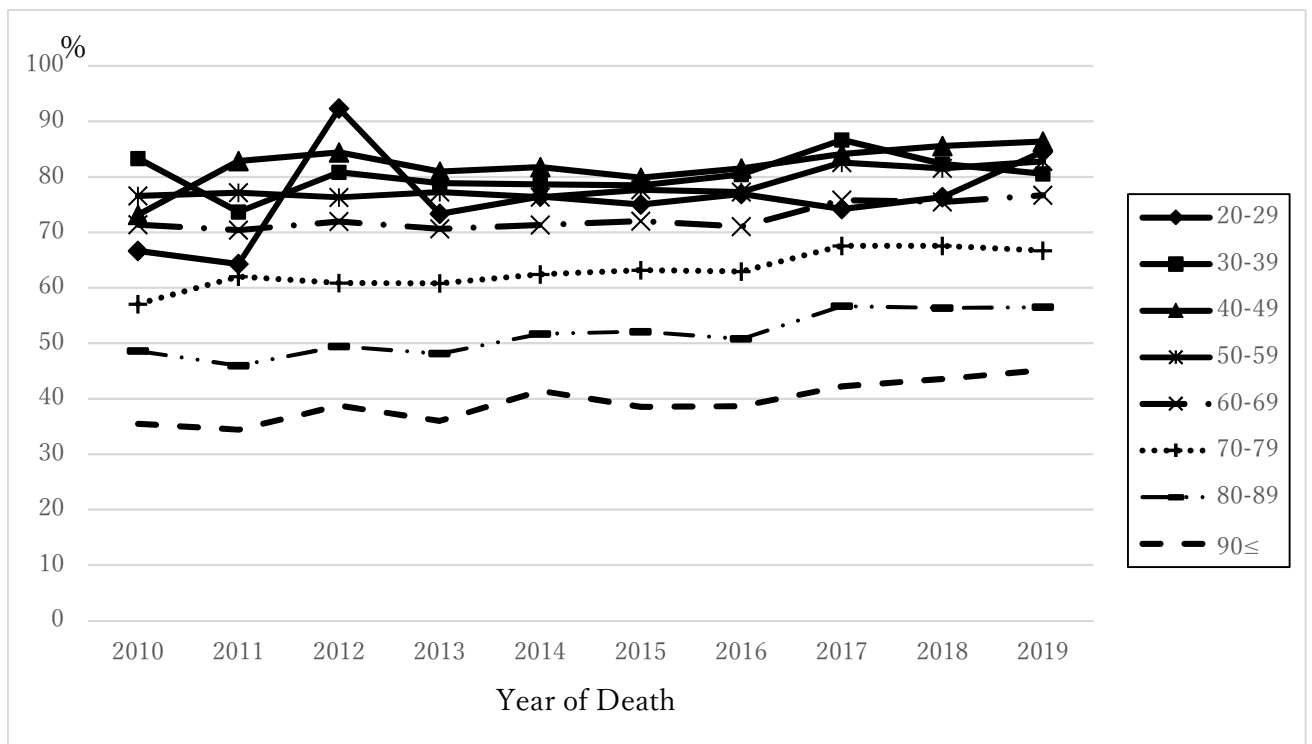


Fig 3. Prescription prevalence (%) of opioids for patients with cancer before death by age group, 2010 to 2019.

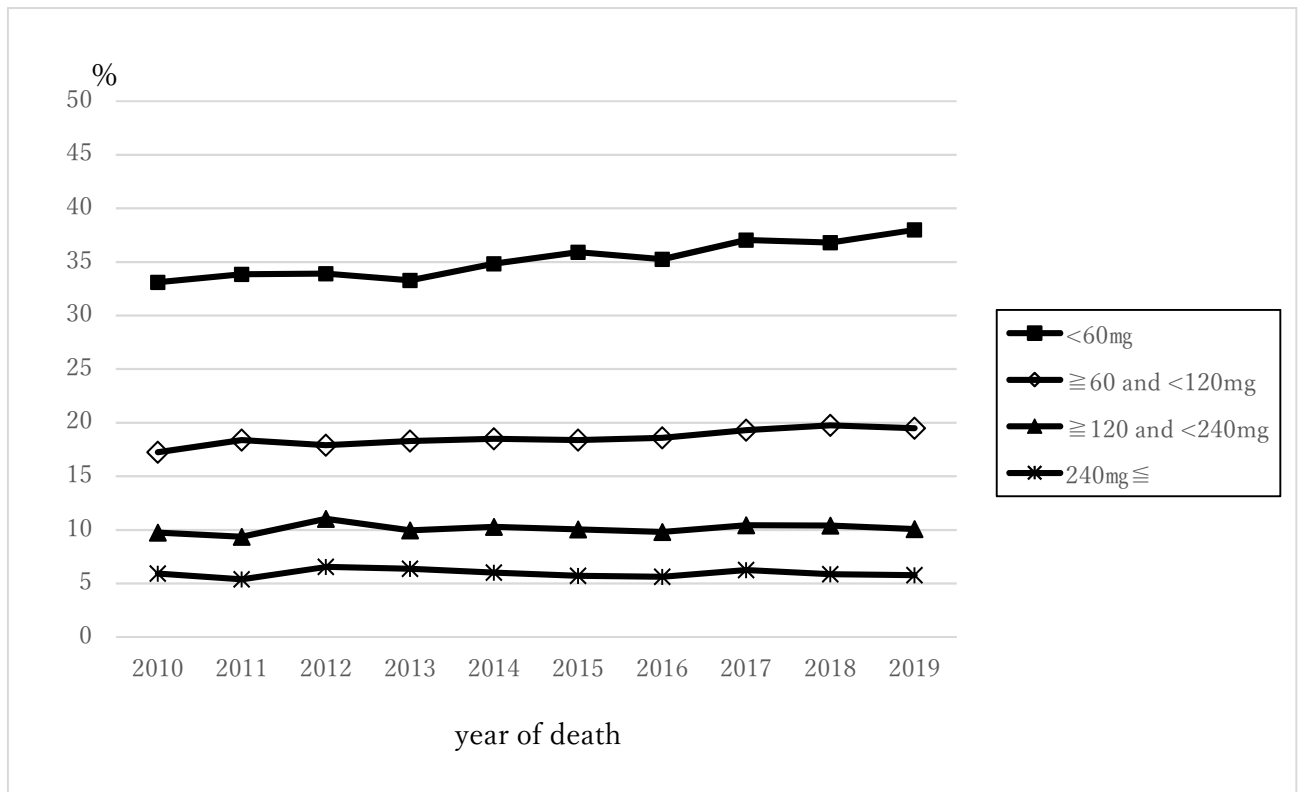


Fig 4. Mean daily opioid dose of OMEQ in the 30 days before cancer death, 2010–2019. OMEQ: the oral morphine equivalents.

Table 1. The DDDs for Opioids.

Name	DDD	Unit	Adm.R
Morphine	0.1	g	O
	30	mg	P
	30	mg	R
Oxycodone	75	mg	O
	30	mg	P
Fentanyl	1.2	mg	TD
	0.6	mg	SL
Hydromorphone	20	mg	O
	4	mg	P

Adm.R=Route of administration, O=oral, P=parenteral, R=rectal, TD=transdermal, SL=sublingual/buccal

Table 2. Characteristics of study population.

Characteristic	No. of patients	%
All	221,598	100
Age at death, years		
20–29	396	0.2
30–39	1,583	0.7
40–49	6,138	2.8
50–59	16,981	7.7
60–69	50,603	22.8
70–79	72,448	32.7
80–89	61,247	27.6
90 ≤	12,202	5.5
Sex		
Male	134,882	60.9
Female	86,716	39.1
Cancer site		
Lung	42,317	19.1
Colorectal	23,634	10.7
Stomach	25,124	11.3
Esophageal	7,059	3.2
Pancreas	23,100	10.4
Breast	6,215	2.8
Prostate	4,940	2.2
Head and neck	3,501	1.6
Brain and neurological	1,541	0.7
Blood	18,635	8.4
Others	65,532	29.6
No. of cancer death by year		
2010	3,976	1.8
2011	6,686	3.0
2012	8,797	4.0

2013	14,643	6.6
2014	22,330	10.1
2015	27,245	12.3
2016	31,327	14.1
2017	34,192	15.4
2018	36,288	16.4
2019	36,229	16.3
<hr/>		
Hospital size, beds		
≤199	15,015	6.8
200–499	103,459	46.7
500≤	59,464	26.8
Palliative care wards	43,660	19.7
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Table 3. Time trends for opioid prescription prevalence for cancer patients before death from 2010 to 2019.

Variables	Any opioid				Morphine				Oxycodone				Fentanyl			
	Slopes	95%CI			Slopes	95%CI			Slopes	95%CI			Slopes	95%CI		
Overall	0.733	0.731	to	0.735	-0.959	-0.961	to	-0.958	1.730	1.728	to	1.732	-0.601	-0.601	to	-0.600
Hospital type																
199 beds or less	0.439	0.426	to	0.452	-0.799	-0.810	to	-0.789	0.722	0.719	to	0.725	0.268	0.256	to	0.280
200–499 beds	-0.314	-0.317	to	-0.311	-1.286	-1.288	to	-1.284	1.201	1.199	to	1.203	-0.519	-0.521	to	-0.518
500 beds and more	-0.255	-0.259	to	-0.250	-1.494	-1.499	to	-1.490	1.564	1.559	to	1.569	-0.773	-0.775	to	-0.772
Palliative care wards	4.880	4.850	to	4.910	0.586	0.567	to	0.606	3.069	3.057	to	3.081	-0.359	-0.367	to	-0.351
Age at death, years																
20–29	0.921	0.721	to	1.122												
30–39	0.613	0.559	to	0.667												
40–49	0.819	0.800	to	0.838												
50–59	0.928	0.919	to	0.937												
60–69	0.837	0.832	to	0.842												
70–79	1.026	1.022	to	1.030												
80–89	1.261	1.255	to	1.266												
90 and over	1.204	1.192	to	1.215												

CI, confidence interval