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ORIGINAL ARTICLE

Incidence and trend of antiresorptive agent-related osteonecrosis of the jaw from 2016 to 2020 in Kure, Japan

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Abstract

Summary We investigated the incidence/trend of osteonecrosis of the jaw by antiresorptive agent dose over a 5-year period in Kure city, Japan. The incidence was 24 times higher among osteoporosis patients with low-dose agents and 421 times higher among cancer patients with high-dose agents than in the population without agents.

Purpose We launched the registry system of osteonecrosis of the jaw (ONJ) cases in 2015 to investigate the trend in ONJ incidence. The purpose of our study was to estimate the ONJ incidence among patients with antiresorptive agent use by dosage and people without antiresorptive agent use in Kure and its trend from 2016 to 2020.

Methods From 2016 to 2021, 98 eligible ONJ patients were enrolled. Medication-related ONJ (MRONJ) was diagnosed based on the American Association of Oral and Maxillofacial Surgeons criteria. The annual number of those with and without antiresorptive agents was obtained from the claims database. Antiresorptive agents used for cancer and osteoporosis patients were defined as high- and low-dose medications, respectively.

Results The annual incidence of high-dose MRONJ was 2305.8 per 100,000 and that of low-dose MRONJ was 132.5 per 100,000, while the ONJ incidence among people without antiresorptive agents was 5.1 per 100,000. The incidence ratio was 23.6 ($p < 0.001$, 95% confidence interval (CI) 13.3–41.8) among osteoporosis patients who used low-dose antiresorptive agents and 420.6 ($p < 0.001$, 95% CI 220.8–801.4) among cancer patients who used high-dose agents compared with people who did not use these agents. MRONJ incidence increased from 2016 to 2020, but the incidence of high-dose MRONJ decreased, although this was nonsignificant.

Conclusion We demonstrated the incidence and trend of ONJ by antiresorptive agent dose over a 5-year period in Kure after launching the multiprofession study. This collaborative study for the early detection and prevention of ONJ will continue.

Keywords ARONJ · BRONJ · Dose dependent · DRONJ · MRONJ

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Introduction

One of the risk factors for osteonecrosis of the jaw (ONJ) is the use of antiresorptive agents for osteoporosis and metastatic bone tumors, and medication-related ONJ is termed MRONJ [1]. MRONJ includes bisphosphonate (BP)-related ONJ (BRONJ) and denosumab (Dmab)-related ONJ (DRONJ). The American Association of Oral and Maxillofacial Surgeons (AAOMS) stated that the risk for MRONJ among osteoporosis patients with BPs was 20–50 per 100,000, and the risk for MRONJ among osteoporosis patients with Dmab was 40–300 per 100,000 [1]. In addition, the risk for MRONJ among cancer patients with high-dose BP ranges from 0 to 18,000 per 100,000, and the risk for MRONJ among cancer patients with high-dose Dmab ranges from 0 to 6900 per 100,000. The incidence of ONJ is greatest in the cancer patient population, in which high-dose BPs/Dmab are used at frequent intervals, and the incidence of ONJ in the osteoporosis patient population has been estimated to be marginally higher than the incidence in the general population [2]. However, there are few publications on the incidence ratio of ONJ among medications (high-dose BPs/Dmab, low-dose BPs/Dmab, and no antiresorptive agents).

We started a population-based study entitled "Kure-DREAMS" (Kure Data-based Results and Evidence Assisted by a Multiprofession Study) in 2015, which aims to prevent osteoporosis, fracture, and osteoporosis-related disorders in collaboration with multiple professions, including physicians, dentists, medical staff, medical societies, and local government in Kure city. Kure city is a regional core city with a population of approximately 210,000 located in Hiroshima, Japan. The percentage of the elderly population aged 65 years and older was 35.4% as of 2020. We launched the project to prevent osteoporosis and fractures among elderly individuals in 2014, and at the same time, medical and dental liaisons were strengthened to prevent and detect ONJ. The ONJ registry was launched in 2015, and the number/trend of ONJ occurrences has been investigated since then.

There are three core hospitals with oral surgeons in this city, and almost all ONJ cases are referred to those three hospitals. In addition, since residents in Japan are obliged to take out medical insurance, the medical claims data are administered by the city and can be examined to ascertain the medical practices that received medication in the area [3, 4]. Using this claims database and the ONJ registry data, we determined the number of ONJ occurrences in each year and the number of patients prescribed antiresorptive agents (high- and low-dose BPs/Dmab). The purpose of this study was to estimate the ONJ incidence and trend among patients who used antiresorptive agents by dosage and people who did not use these agents in Kure and its trend from 2016 to 2020.

Methods

Study population

The study population was residents aged 40 years and older in Kure who were insured by the National Health Insurance (NHI) and the Senior Elderly Care System (SECS). We obtained medical information with respect to sex, age range (40–59, 60–69, 70–79, ≥ 80) and the number of patients prescribed antiresorptive agents from the NHI/SECS database of the city government. Aggregated data by age and sex in tabular form from 2016 to 2020 were provided by the city government. Antiresorptive agents used for metastatic bone tumors were defined as high-dose BPs/Dmab, and those used for osteoporosis were defined as low-dose BPs/Dmab. The number of people with prescriptions for each medication (high-dose BPs, high-dose Dmab, low-dose BPs, and low-dose Dmab) was calculated based on medication codes from each insurance database (Supplementary Table 1). Patients who were prescribed antiresorptive agents at least once within a fiscal year were counted as one person-year. The last medication administered during the year was prioritized; for example, patients who changed from Dmab to BP were defined as BP medication patients, and patients who changed from BP to Dmab were defined as Dmab medication patients. The population without antiresorptive agents remained after subtracting patients who were prescribed antiresorptive agents from the whole study population. This population included (1) untreated osteoporosis patients regardless of whether they were diagnosed with osteoporosis; (2) those with osteoporosis who were treated with teriparatide (TPTD), romosozumab (ROMO), a selective estrogen receptor modulator (SERM), and/or vitamin D metabolites; and 3) those without osteoporosis.

Patients diagnosed with ONJ

The ONJ registry was launched in collaboration with general dentists and oral surgeons in three core hospitals in Kure in 2015. The following information was registered: date of ONJ diagnosis, age, sex, site of occurrence, ONJ stage, treatment and outcome. A total of 138 patients were diagnosed with ONJ, excluding stage 0, from April 2016 to March 2021. Those living outside of Kure city ($n = 27$), those diagnosed with MRONJ and insured by a health insurance system other than the NHI and the SECS ($n = 7$), those with unavailable medication information ($n = 3$), those with radiation therapy for the jaw ($n = 2$), and those with an onset at less than

40 years ($n=1$) were excluded from our study. Excluding the above 40 ONJ cases, 98 ONJ cases were included in the analysis. The diagnostic criteria for MRONJ were in accordance with those in the position paper from the Allied Task Force Committee of the Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology and JSOMS [5], in which definition and diagnostic criteria were the same as those from the American Association of Oral and Maxillofacial Surgeons (AAOMS) [1], and patients were diagnosed with ONJ if the other two criteria were met even if no antiresorptive agents were used.

Statistical analysis

We calculated the incidences of ONJ among people who did not use antiresorptive agents and among patients prescribed each antiresorptive agent each year. After calculating the incidence of ONJ for each year, Poisson regression was performed using STATA/IC 16 (StataCorp, College Station, TX, USA). The trend analysis for ONJ incidence from 2016 to 2020 was performed using Poisson regression analysis with 2016–2020 as a dependent variable, the natural logarithm of person-years as an offset, and the number of ONJ cases in each year as the independent variable. In addition, the linear model regarding risk factors included the natural logarithm of the number of ONJ cases as a response variable, the natural logarithm of person-year as an offset, indicators for antiresorptive agent dose (none, low dose, high dose) as main explanatory variables, and indicators for sex (male, female), age range (40–59, 60–69, 70–79, ≥ 80), and year (2016, 2017, 2018, 2019, 2020) as covariates. All estimates were transformed from the logarithmic to the natural scale and were reported as incidence ratios (IRs) [6]. *P* values < 0.05 were considered statistically significant.

Our study was approved by the Ethics Committee of Kure Nakadori Hospital (approval number, 2022–01) and conducted in Kure city (Hiroshima, Japan) from April 2016 to March 2021.

Results

Demographic data in Kure

Demographic data for Kure are shown in Table 1. The number of prescriptions for antiresorptive agents for residents aged 40 and older tended to increase each year. Among them, the number of prescriptions for high-dose Dmab increased, while the number of prescriptions for high-dose BPs decreased (Fig. 1). Of the population without antiresorptive agents, 6.5%, 1.8%, 0.8%, and 0.1% received prescriptions for vitamin D metabolites only, SERMs, TPTD, and ROMO, respectively.

Table 1 Demographic data in Kure city from 2016 to 2020

	2016	2017	2018	2019	2020
Residents aged > 40 years					
Number insured by NHI and SECS, *n*	80,947	80,168	79,588	78,826	77,752
Male, *n* (%)					
40 y–59 y	4209 (5.2)	4076 (5.1)	4022 (5.1)	3988 (5.1)	3890 (5.0)
60 y–69 y	8598 (10.6)	8043 (10.0)	7229 (9.1)	6512 (8.3)	5710 (7.3)
70 y–79 y	12,408 (15.3)	12,632 (15.8)	13,035 (16.4)	13,512 (17.1)	13,812 (17.8)
≥ 80 y	8180 (10.1)	8447 (10.5)	8704 (10.9)	8723 (11.1)	8831 (11.4)
Female, *n* (%)					
40 y–59 y	4403 (5.4)	4102 (5.1)	4035 (5.1)	3940 (5.0)	3772 (4.9)
60 y–69 y	11,175 (13.8)	10,573 (13.2)	9390 (11.8)	8517 (10.8)	7559 (9.7)
70 y–79 y	15,685 (19.4)	15,731 (19.6)	16,272 (20.4)	16,734 (21.2)	17,250 (22.2)
≥ 80 y	16,289 (20.1)	16,564 (20.7)	16,901 (21.2)	16,900 (21.4)	16,928 (21.8)
Prescription					
No antiresorptive agent, *n* (%)	71,950 (88.9)	70,924 (88.5)	70,229 (88.2)	69,251 (87.9)	68,059 (87.5)
High-dose antiresorptive agents, *n* (%)	156 (0.2)	164 (0.2)	167 (0.2)	168 (0.2)	169 (0.2)
High-dose BP, *n*	105	94	85	75	76
High-dose Dmab, *n*	51	70	82	93	93
Low-dose antiresorptive agents, *n* (%)	8841 (10.9)	9080 (11.3)	9192 (11.6)	9407 (11.9)	9524 (12.3)
Low-dose BP, *n*	6399	6528	6602	6755	6927
Low-dose Dmab, *n*	2442	2552	2590	2652	2597

NHI National Health Insurance, *SECS* Senior Elderly Care System; BP, bisphosphonate; Dmab, denosumab

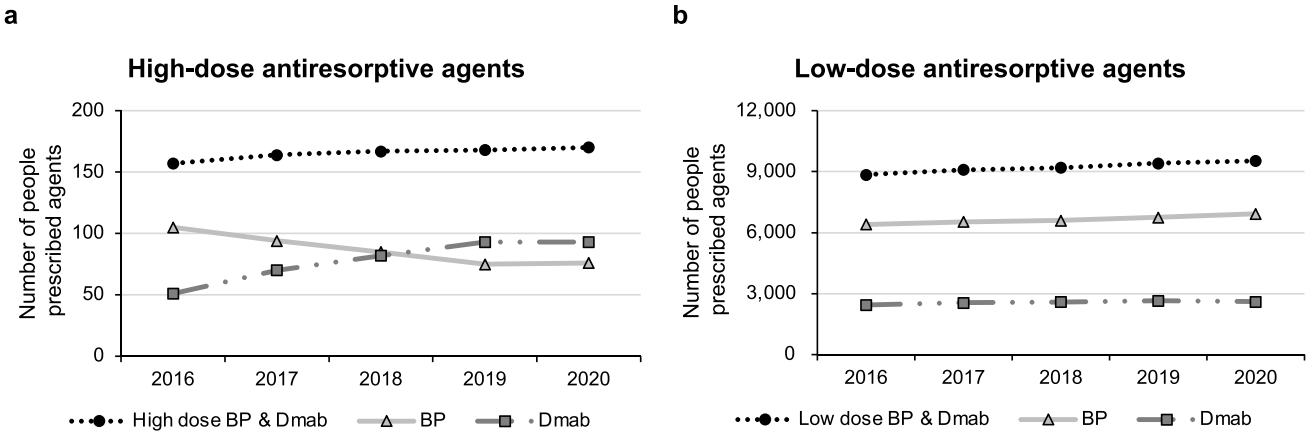

Fig. 1 Number of people prescribed antiresorptive agents every year. The number of people prescribed **a** high-dose and **b** low-dose antiresorptive agents among residents aged 40 and older tended to increase each year. Among them, the number of prescriptions for high-dose Dmab increased, while the number of prescriptions for high-dose BPs showed a downward trend. Dmab denosumab, BP bisphosphonate

Incidence of ONJ in Kure city

The annual incidence of ONJ in Kure by calendar year is shown in Table 2. Overall, there was an upward trend in the incidence of ONJ ($p = 0.016$, IR 1.19, 95% confidence interval (CI) 1.03–1.37). The ONJ incidence tended to increase in the population without antiresorptive agents ($p = 0.023$, IR 1.50, 95% CI 1.05–2.13) throughout the entire period from 2016 to 2020. However, the incidence in 2020 was lower than that in 2019. On the other hand, the

Table 2 ONJ incidence and trend in Kure city from 2016 to 2020

	2016	2017	2018	2019	2020	2016–2020	*p* value for trend*
All ONJ							
Number	12	15	20	31	20	98	
Incidence per 100,000	14.8	18.7	25.1	39.3	25.7	24.7	0.016
High-dose MRONJ							
Number	4	5	4	3	3	19	
Incidence per 100,000	2564.1	3048.8	2395.2	1785.7	1775.1	2305.8	0.446
BP							
Number	2	3	0	1	1	7	
Incidence per 100,000	1904.8	3191.5	0	1333.3	1315.8	1609.2	
Dmab							
Number	2	2	4	2	2	12	
Incidence per 100,000	3921.6	2857.1	4878.0	2150.5	2150.5	3084.8	
Low-dose MRONJ							
Number	8	8	10	22	13	61	
Incidence per 100,000	90.5	88.1	108.8	233.9	136.5	132.5	0.072
BP							
Number	6	6	6	19	8	45	
Incidence per 100,000	93.8	91.9	90.9	281.3	115.5	135.5	
Dmab							
Number	2	2	4	3	5	16	
Incidence per 100,000	81.9	78.4	154.4	113.1	192.5	124.7	
ONJ without BP/Dmab							
Number	0	2	6	6	4	18	
Incidence per 100,000	0	2.8	8.5	8.7	5.9	5.1	0.023

*Trend analysis in ONJ incidence (all ONJ, high-dose MRONJ, low-dose MRONJ, and ONJ without BP/Dmab) from 2016 to 2020 was performed using Poisson regression analysis. *ONJ* osteonecrosis of the jaw, *BP* bisphosphonate, *Dmab* denosumab, *MRONJ* medication-related ONJ

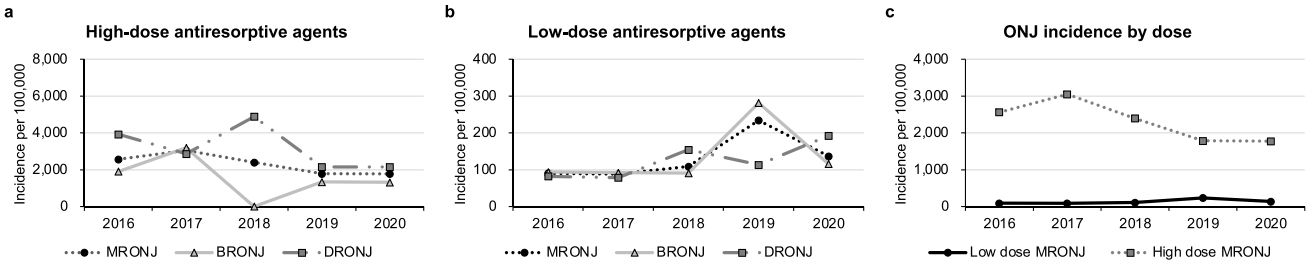

Fig. 2 MRONJ incidence per year. The incidence of **a** high-dose MRONJ, **b** low-dose MRONJ, and **c** MRONJ by dose in Kure city. The incidence of high-dose MRONJ showed a downward trend from 2016 to 2020. ONJ osteonecrosis of the jaw, BP bisphosphonate, Dmab denosumab, MRONJ medication-related ONJ, BRONJ BP-related ONJ, DRONJ Dmab-related ONJ

incidence of high-dose MRONJ was 2305.8 (range, 1775.1 to 3048.8) per 100,000 over the 5-year period and seemed to be decreasing, although this was not statistically significant ($p = 0.446$, IR 0.88, 95% CI 0.64–1.22) (Table 2 and Fig. 2). The incidence of low-dose MRONJ was approximately 132.5 (range, 88.1 to 233.9) per 100,000 over 5 years, and the incidence of ONJ without antiresorptive agent use was the lowest at 5.1 (range, 0 to 8.7) per 100,000. In addition, there was one ONJ patient who used vitamin D metabolites only, and no ONJ patient used SERMs, TPTD, or ROMO from 2016 to 2020.

Poisson regression analysis revealed that the IRs increased with increasing doses of antiresorptive agents after adjusting for sex, age, and fiscal year (Table 3). The IR was 23.6 ($p < 0.001$, 95% CI 13.3–41.8) in the population that used low-dose antiresorptive agents and 420.6 ($p < 0.001$, 95% CI 220.8–801.4) in the population that used high-dose antiresorptive agents compared with the population that did not use antiresorptive agents (Table 3). The incidence of ONJ with high-dose antiresorptive agents was 18 times higher ($p < 0.001$, 95% CI 10.0–31.8) than that with low-dose antiresorptive agents. The trends from 2016 to 2020 for ONJ incidence by medication dose are shown in Table 4. The IR of ONJ among cancer patients treated with high-dose antiresorptive agents appeared to decrease from year to year, although the difference was not statistically significant. Among osteoporosis patients treated with low-dose antiresorptive agents, there was a temporary increase in ONJ incidence in 2019. In the population without antiresorptive agents, approximately 10% were osteoporosis patients

Table 3 Trends in ONJ incidence from 2016 to 2020

	IR	SE	95% confidence interval	*P* value*
Sex				
Male	Reference	-	-	-
Female	0.97	0.25	0.59–1.60	0.909
Age				
40–59	Reference	-	-	-
60–69	1.39	0.89	0.39–4.90	0.611
70–79	1.02	0.63	0.30–3.40	0.979
≥ 80	1.29	0.79	0.39–4.27	0.682
Antiresorptive agents				
None	Reference	-	-	-
Low dose	23.6	6.9	13.3–41.8	< 0.001
High dose	420.6	138.3	220.8–801.4	< 0.001
Year				
2016	Reference	-	-	-
2017	1.22	0.47	0.57–2.61	0.608
2018	1.62	0.59	0.79–3.31	0.187
2019	2.49	0.85	1.28–4.85	0.007
2020	1.59	0.58	0.78–3.26	0.203

*Trends in ONJ incidence from 2016 to 2020 were evaluated using Poisson regression analysis, adjusting for sex, age range, medication dose and year. *P* values < 0.05 were considered statistically significant. *ONJ* osteonecrosis of the jaw, *IR* incidence ratio, *SE* standard error

Table 4 Trends in ONJ incidence by medication dose from 2016 to 2020

	High-dose antiresorptive agents				Low-dose antiresorptive agents			
	IR	SE	95% CI	P value*	IR	SE	95% CI	*P* value*
Sex								
Male	Reference	-	-	-	Reference	-	-	-
Female	1.38	0.65	0.55–3.46	0.498	1.06	0.43	0.48–2.34	0.888
Age								
40–59	Reference	-	-	-	Reference	-	-	-
60–69	0.25	0.25	0.04–1.82	0.172	1.26	1.33	0.16–10.0	0.826
70–79	0.47	0.38	0.10–2.26	0.344	0.24	0.25	0.03–1.90	0.177
≥ 80	0.52	0.42	0.11–2.56	0.422	0.56	0.57	0.08–4.10	0.567
Year								
2016	Reference	-	-	-	Reference	-	-	-
2017	1.22	0.82	0.33–4.54	0.771	0.98	0.49	0.37–2.62	0.973
2018	0.94	0.67	0.23–3.77	0.926	1.22	0.58	0.48–3.10	0.670
2019	0.69	0.53	0.15–3.13	0.633	2.67	1.10	1.19–6.01	0.017
2020	0.71	0.55	0.16–3.21	0.658	1.43	0.65	0.58–3.51	0.431

*Trends in ONJ incidence by medication dose from 2016 to 2020 were evaluated using Poisson regression analysis, adjusting for sex, age range and year. *P* values < 0.05 were considered statistically significant. *ONJ* osteonecrosis of the jaw, *IR* incidence rate ratio, *SE* standard error, *CI* confidence interval

treated with medications other than antiresorptive agents. We performed an additional subanalysis in the treated osteoporosis population to assess the risk of ONJ incidence by medication. A subanalysis showed that osteoporosis patients who used low-dose antiresorptive agents had an ONJ incidence rate approximately 30 times higher than that of osteoporosis patients who used vitamin D metabolites (Table 5). The incidence ratio among patients with low-dose BP was similar to that among those with low-dose Dmab.

Table 5 ONJ incidence ratio by medication among osteoporosis patients

	IR	SE	95% confidence interval	*P* value*
Sex				
Male	Reference	-	-	-
Female	1.09	0.44	0.49–2.41	0.829
Age				
40–59	Reference	-	-	-
60–69	1.27	1.34	0.16–10.03	0.823
70–79	0.27	0.28	0.03–2.10	0.210
≥ 80	0.57	0.58	0.08–4.20	0.583
Medications				
Vitamin D	Reference	-	-	-
Bisphosphonate	34.5	34.9	4.8–250.8	< 0.001
Denosumab	32.1	33.1	4.2–242.8	0.001
Year				
2016	Reference	-	-	-
2017	0.98	0.49	0.37–2.62	0.972
2018	1.35	0.63	0.54–3.35	0.522
2019	2.67	1.10	1.19–6.01	0.017
2020	1.43	0.65	0.58–3.51	0.431

*Trends in the ONJ incidence from 2016 to 2020 among osteoporosis patients who used vitamin D, bisphosphonate, and denosumab were evaluated using Poisson regression analysis, adjusting for sex, age range, medications, and year. *P* values < 0.05 were considered statistically significant. *ONJ* osteonecrosis of the jaw, *IR* incidence ratio, *SE* standard error

Discussion

We established the registration system for ONJ in 2015 and consecutively enrolled 98 eligible ONJ patients between April 2016 and March 2021 at three core hospitals in Kure city. The incidence of high-dose MRONJ was 2305.8 (range, 1775 to 3049) per 100,000 over the 5-year period, that of low-dose MRONJ was 132.5 (range, 88 to 234) per 100,000, and that of ONJ without antiresorptive agents was the lowest at 5.1 (range, 0 to 8.7) per 100,000. The strength of this study was in determining the incidence of ONJ by the dose of each antiresorptive agent based on the ONJ registry, in which precise diagnoses were made by ONJ specialists for residents insured by two kinds of insurance systems.

The results of a nationwide population-based study in Japan on ONJ were reported by Ishimaru et al. [7] in 2022. The prevalence was 0.06%, and the incidence rate was 22.9 per 100,000 person-years among patients with osteoporosis; the prevalence was 1.47%, and the incidence rate was 1231.7 per 100,000 person-years among patients with cancer [7]. Their and our reported ONJ incidences appeared to be roughly consistent with the results presented by the International Task Force and an AAOMS position paper published

in 2022 [1, 2]. However, the ONJ incidence in our investigation is likely to be higher than that reported by Ishimaru et al. [7] for both high- and low-dose antiresorptive agents. There were several reasons for these differences, one of which would be the difference in the way ONJ cases were extracted: their data were based entirely on the claims database [7], whereas we directly counted those cases diagnosed by dentists using the ONJ registry. Our study might provide an almost complete count of ONJ cases that occurred over a 5-year period, while the incidence by Ishimaru et al. [7] may be an overestimate/underestimate because the survey was based on the claims database, in which the definitions of ONJ differ between each hospital. In addition, the nationwide population-based study included only patients who had newly begun using antiresorptive drugs, while our study did not take into account the duration of medication use, so the proportion of patients who took the drug for longer periods might be higher in our study. Taking antiresorptive drugs for longer periods (> 4 years) was reported to be a risk factor for ONJ occurrence [1, 8, 9], which may be one of the reasons for the higher incidence of ONJ in our study.

The KureDREAMS project on ONJ prevention in Kure city, which began in 2015, has led to early detection of ONJ [10] and might be one of the reasons for the high incidence rate of ONJ in Kure city. The central committee for the adequate treatment of osteoporosis (A-TOP) research group has recommended a forum to share information about ONJ among medical professionals, dentists, and patients [11]. The Kure City Dental Association and the three major oral surgery practices in Kure city work closely together, as well as among dentists, making it easy to detect cases of ONJ early. In addition, the Kure City Dental Association regularly disseminates information on MRONJ and osteoporosis through workshops and the media as medical and dental liaisons. However, further investigations are needed to determine whether such collaboration will truly lead to the early detection of ONJ in the future. The ONJ registry started in Germany when cases of low-dose BRONJ were reported in 2004 [12], and medical-dental liaisons and patient education began [13]. However, there were no investigations showing a trend in ONJ incidence, and to the best of our knowledge, the results of our study are the first report of secular trends after the launch of the ONJ registry. The KureDREAMS project on ONJ prevention in Kure city, as in other countries and in the future, is expected to detect earlier stages of MRONJ and to reduce its incidence rate.

Osteoporosis patients and people without antiresorptive agents showed an upward trend in ONJ incidence, which may be due to the increased interest in ONJ since the ONJ registry was launched in Kure city. On the other hand, the incidence of ONJ from 2017 to 2020 showed a downward trend among cancer patients in Kure city, although this was not statistically significant; the incidence peaked in 2017 and declined from 3048.8 per 100,000 to 1775.1 per 100,000. One potential interpretation is that medical-dental liaisons have progressed because of the introduction of the "perioperative oral function management fee," which began in 2012 to reduce complications after cancer surgeries. Thus, the incidence of MRONJ among osteoporosis patients would also decrease in the future, as medical and dental liaisons have been strengthened to prevent and detect ONJ since 2015.

To the best of our knowledge, the incidence of ONJ in the population without antiresorptive agents based on the registration system adopted in our study was the first report worldwide and was higher than we expected. Since the reason for ONJ without antiresorptive agents was mostly periapical periodontitis in our study (data not shown), continuous bacterial infection of the jaw by inadequate oral hygiene management was considered to be the major cause in these cases, as previous studies have shown [14]. Poor hygiene management factors in Kure city included the following: patient factors (lack of interest in oral care), dental factors (worsening of dental disease due to delay in tooth extractions), and geographical factors (Kure city contains many small islands whose residents have limited means of transportation). In Japan, the percentage of edentulous individuals is low among countries worldwide because of the custom of trying to preserve teeth [15]. The number of extracted teeth is reported to be a risk factor for ONJ occurrence [7]; however, the cause of ONJ would be continuous bacterial infection of the jaw preceding tooth extraction and not tooth extraction itself. Therefore, we consider striving to preserve as many healthy teeth as possible through regular oral hygiene maintenance to be important.

The International Task Force on Osteonecrosis of the Jaw mentioned that the incidence of osteoporosis-related ONJ was only slightly higher than that observed in the general population, but it did not indicate actual ONJ incidence in the general population [2]. ONJ in the population that does not take antiresorptive agents is rare, but the number of reported cases has increased in recent years [16]. However, systematic reviews of ONJ related to nonantiresorptive medications were performed among cancer patients receiving nonantiresorptive agents, not community residents, as we performed in this study [17]. In our study, the ONJ incidence in the population without antiresorptive agents was 5.1 per 100,000, and the incidence of osteoporosis-related ONJ was approximately 24 times higher than that of ONJ in the population. This was also the first report to simultaneously compare the incidence of ONJ among cancer and osteoporosis patients and the general population, clearly demonstrating the extent to which the administration of antiresorptive agents increases the risk of developing ONJ. This study suggested that ONJ prevention is necessary when using antiresorptive agents, and it would be interesting to see how much the incidence of ONJ can be reduced through collaboration for ONJ prevention in Kure city in the future.

The population without antiresorptive agents in this study mainly consisted of those without osteoporosis and partly included untreated osteoporosis patients and treated osteoporosis patients with medications except antiresorptive agents, of whom approximately 6.5% used active vitamin D metabolite medication (oral alfacalcidol, eldecalcitol, and calcitriol) only. Active vitamin D is prescribed for osteoporosis, chronic kidney disease, hypoparathyroidism, and other disorders of vitamin D metabolism in Japan. Although other indications besides osteoporosis might be included in the population who used vitamin D metabolites, we considered that it would be mostly osteoporosis patients. Two previous large observational databases suggested that osteoporosis itself, rather than antiresorptive agents, is a risk factor for ONJ [18, 19], and thus, we performed an additional subanalysis in the population with osteoporosis. The ONJ incidence rate was approximately 30 times higher among osteoporosis patients using low-dose antiresorptive agents than among osteoporosis patients using vitamin D metabolites (Table 5). An AAOMS position paper in 2022 stated that the risk of ONJ among patients with Dmab was almost an order of magnitude higher than that for patients with BPs [1]. However, no difference in the ONJ incidence was found between patients with BP and Dmab in Kure (Table 5). Our study selected osteoporosis patients who used vitamin D metabolites as the control group, whereas a previous study selected osteoporosis patients who used SERMs as controls [18]. The review organized by the European Calcified Tissue Society (ECTS) stated that there is weak evidence for the role of vitamin D deficiency in MRONJ development [16]. Active vitamin D medication might have prevented ONJ development in our study. No ONJ cases developed among osteoporosis patients treated with TPTD, ROMO, or SERMs.

In our study, the number of prescriptions for high-dose Dmab increased, while the number of prescriptions for high-dose BPs decreased. There are potential reasons for the increased number of high-dose Dmab prescriptions: (1) there have been reports showing that denosumab is significantly more effective against skeletal-related events than zoledronate [20]; (2) denosumab is able to be used for cancer patients with severe renal dysfunction; and (3) denosumab is injected subcutaneously, which reduces the burden on the patients compared to intravenous zoledronic acid. For the above potential reasons, Japanese surgeons and physicians have tended to prefer high-dose Dmab over high-dose BPs for cancer patients in recent years. In contrast, since an AAOMS position paper in 2022 reported that the risk for MRONJ among cancer patients exposed to high-dose Dmab is comparable to the risk of MRONJ among cancer patients exposed to high-dose BP [1], the trend in the number of prescriptions for high-dose Dmab/BP would not have affected the trend in ONJ incidence in Kure city.

There were several limitations in our study. The first was that ONJ cases in our study were identified at three facilities in Kure city; thus, ONJ cases diagnosed at other facilities were not counted. However, only these three hospitals have oral surgeons in this city, and patients with potential ONJ are referred to these three hospitals, even if the patients first visit a dental clinic or another hospital. Second, our study was based on local claims data and the ONJ registry in Kure city, which might not be representative of the incidence and overall trend in Japan. Third, since patients who had at least one prescription during the fiscal year were defined as "having a prescription," this might lead to an underestimation of the MRONJ incidence due to the larger denominator value. Fourth, it is known that MRONJ in the osteoporosis population emerges after more than 3 or 4 years of BP exposure [1], and MRONJ incidence increases with time of exposure to BPs. The database included individual data that were unavailable, and thus, it was difficult to analyze individual information considering the duration of BP use, which was a limitation in our investigation.

In conclusion, we investigated the incidence and trend of ONJ by dose of antiresorptive agents over a 5-year period in Kure city. The annual incidence of high-dose MRONJ was 2305.8 per 100,000, that of low-dose MRONJ was 132.5 per 100,000 and that of ONJ without antiresorptive agents was 5.1 per 100,000, which was higher than those reported in previous studies. The ONJ incidence ratio was 23.6 among the osteoporosis patients using low-dose antiresorptive agents and 420.6 among the cancer patients using high-dose antiresorptive agents compared with the population that did not use antiresorptive agents. This was the first report to simultaneously assess the incidence of ONJ with antiresorptive agents based on the ONJ registry. Overall, the MRONJ incidence increased from 2016 to 2020, but the incidence of high-dose MRONJ seemed to decrease, although the difference was not statistically significant. This fact-finding investigation began with efforts to prevent the onset of ONJ, and we should continue this work for the early detection and prevention of ONJ in the future.

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Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institu-

tional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Formal consent is not required for this type of study.

Conflict of interest N. Okimoto received consulting fees from Asahi-Kasei Pharmaceutical Co., Ltd. and Teijin Pharma Ltd. N. O received payments for lectures, including speakers' bureau fees, from Asahi-Kasei Pharmaceutical Co., Ltd.; Amgen K. K.; Chugai Pharmaceutical Co.; Daiichi-Sankyo Co. Ltd.; Eli Lilly Japan.; and Teijin Pharma Ltd. S. Fujiwara received consulting fees from Asahi-Kasei Pharmaceutical Co., Ltd. T. Kunihara, H. Tohmori, M. Tsukamoto, M. Kobayashi, T. Okumura, H. Teramoto, T. Hamasaki, T. Yamasaki, and T. Nakagawa declare that they have no conflict of interest.

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