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Incidence of skeletal-related events in patients with breast or prostate cancer-induced bone metastasis or multiple myeloma: A 12-year longitudinal nationwide healthcare database study

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ABSTRACT

Background: This study examined the incidence of skeletal-related events (SRE) among patients with breast cancer (BC)- or prostate cancer (PC)-induced bone metastasis or multiple myeloma (MM) based on a population-based, 12-year healthcare database.

Methods: Patients aged ≥18 years with bone metastasis from BC or PC or with MM between 2004 and 2015 were included. SRE was defined as pathologic fracture, spinal cord compression, radiation, or surgery to bone. Patients were followed-up from the initial diagnosis of bone metastasis (for those with BC or PC) or MM until SRE occurrence. To estimate multiple SREs, we applied a 21-day time window to ensure that subsequent SREs occurred independently from the previous event. We calculated the incidence and 95% confidence intervals (CIs), stratified according to the previous SRE history.

Results: Our cohort included 53,231 patients, including 23,811 with BC, 19,170 with PC, and 10,250 with MM. The incidence of multiple SREs in the 21-day time window was 1.03 (95% CI = 1.01–1.05) in patients with previous SRE history and 0.19 (95% CI = 0.19–0.20) in those without. The cumulative SRE incidences were 47%, 31.4%, and 38.0% in BC, PC, and MM patients.

Conclusion: The incidences of multiple SREs in BC- or PC-induced bone metastasis or MM in this 12-year South Korean cohort were slightly higher than those in European countries. Our study provided real-world evidence that patients with BC- or PC-induced bone metastasis or MM are at high risk of SRE.

1. Introduction

The bone is a preferred site for metastasis due to the presence of adhesive molecules on the surface of tumor cells, the production of angiogenic factors, and the presence of bone resorbing factors that foster tumor growth [1–3]. Metastasis to the bone is common in advanced cancer [4,5] including breast cancer (BC), prostate cancer (PC), and multiple myeloma (MM). Skeletal-related events (SREs) are frequent complications associated with bone metastasis and include pathologic fractures, spinal cord compression, radiation, or surgery to bone [6]. Bone metastasis may upset skeletal homeostasis by disturbing the equilibrium between osteoblastic bone formation and osteoclast-mediated bone destruction [7], triggering SREs. SREs in patients with advanced cancer may lead to decreased survival and substantial morbidity [8]. In previous studies of patients with either BC- or PC-induced bone metastasis, a higher risk of mortality was associated with the occurrence of SREs in BC (hazard ratio [HR] = 6.2, 95% confidence interval [CI] 5.9–6.5) and PC (HR = 10.2, 95% CI = 9.8–10.7) than that in patients without SREs with BC (HR = 4.9, 95% CI 4.7–5.1) and with PC (HR = 6.6, 95% CI = 6.4–6.9) [9,10].

Patients with bone metastases from BC or PC or with MM are at high risk for bone-related complications. The incidence of the first and multiple SREs in patients with bone metastasis are up to 0.63 [9–12] and 3.9 [13], respectively. MM is the most frequent cancer involving the bones [14,15] and nearly 90% of patients with MM develop osteolytic bone lesions [16]. Since the risk of subsequent SREs increases following an initial SRE [17], the identification of a history of SREs and the events that occur after the initial SRE are important for the estimation of SRE incidence. However, to our knowledge, neither previous SRE status [9–11] nor the rate of subsequent SREs after an initial event [12] have been measured, thereby precluding a comprehensive evaluation of SREs.

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Hence, we used a 12-year longitudinal nationwide healthcare database to investigate SRE incidence in Korea. Our objective was to estimate the incidence of both initial and multiple SREs in patients with BC- or PC-induced bone metastasis or with MM according to SRE history.

2. Methods

2.1. Database

We used a population-based nationwide health insurance claims database established by the National Health Insurance Service of South Korea. The National Health Insurance program attained universal coverage of the population in 1989 [18] and the database contains the healthcare records of approximately 50 million South Koreans. We obtained the claims data for all patients diagnosed with BC, PC, or MM from January 1, 2003, to December 31, 2015. The database contained demographic information such as age and sex, as well as clinical information from both inpatient and outpatient settings. The diagnoses were coded based on the International Classification of Disease, 10th revision (ICD-10). We included patients from the entire Korean population who met our inclusion criteria. We selected our study subjects according to the criteria described in previous clinical trials [19,20] that evaluated SRE incidence in patients with BC- or PC-induced bone metastasis or MM.

2.2. Study population

We recruited patients diagnosed with BC (ICD-10: 'C50'), PC (ICD-10: 'C61'), or MM (ICD-10: 'C90') between January 1, 2003, and December 31, 2015 (Fig. 1). Among patients with BC or PC, we included those who developed bone metastasis (ICD-10: 'C795') after the diagnosis of BC or PC. The index date was defined as the date of the first diagnosis of bone metastasis for BC or PC patients and that of MM for MM patients. We used one-year healthcare utilization records prior to the index date to assess previous SRE history.

We excluded patients who: (i) had missing data on age or sex; (ii) were aged less than 18 years; (iii) had any cancer during the eligibility period between January 1, 2003, and December 31, 2003; (iv) had any cancer other than BC, PC, or MM during the year prior to the index date to ensure that the primary site was either BC, PC, or MM; (vi) had multiple records of two or more cancers among BC, PC, or MM to ensure that each cohort was mutually exclusive; (vii) whose eligibility period was less than one year to ensure that all patients were observed for at least one year to confirm that they met the enrollment criteria; and (viii) were diagnosed with bone metastasis prior to BC or PC to ensure that it was BC- or PC-induced bone metastasis. After exclusion, patients with BC- or PC-induced bone metastasis or MM selected from the National Health Insurance database comprised our overall cohort to evaluate the SRE incidence between 2004 and 2015.

2.3. Definition of SREs

Our outcome, SREs, was defined as pathologic fractures (ICD-10: 'S12', 'S72', 'S32', 'M800', 'M844', 'M907', 'S220', 'S221', 'S525', and 'S526'), spinal cord compression (ICD-10: 'M439', 'M485', 'M495', 'G952', and 'G958'), radiation (procedure code: 'HD052', 'HD055', 'HD053', 'HD056', 'HD061', 'HZ271', 'HD111', and 'HD112'), or surgery to the bone (S2) [11,21].

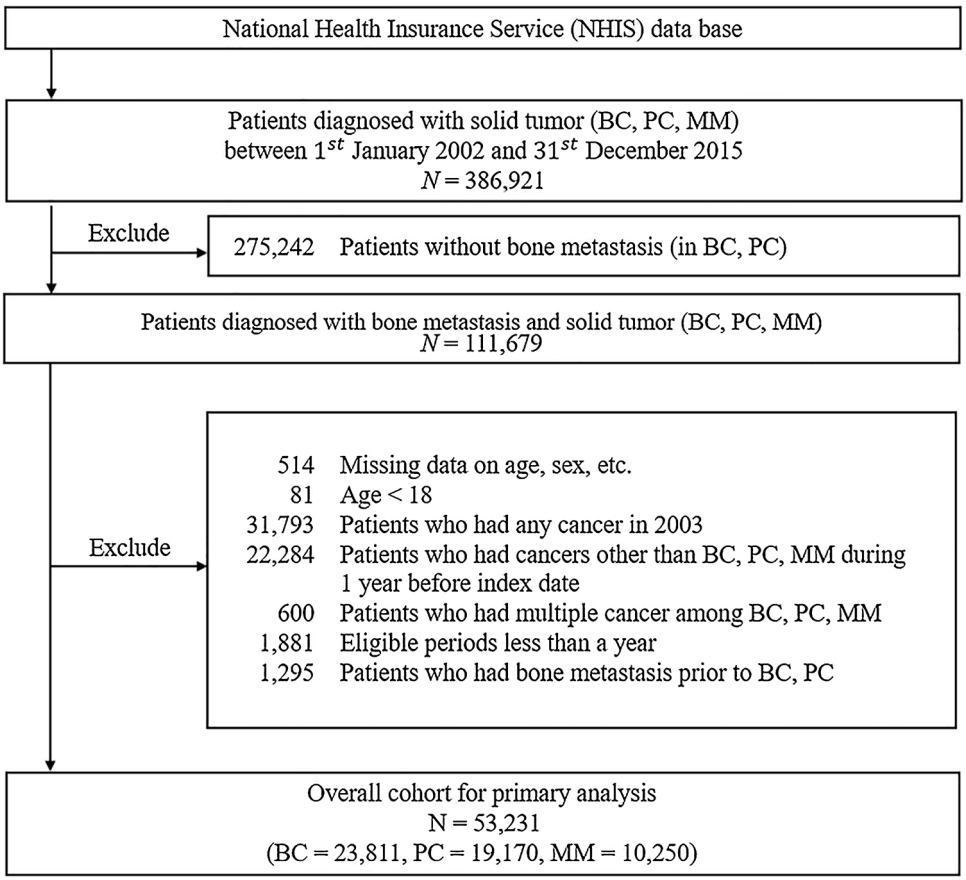

Fig. 1. Flow diagram describing the selection of study subjects from the National Health Insurance database. *The index date was defined as either the date of first bone metastasis diagnosis for those with breast cancer (BC) or prostate cancer (PC) or of multiple myeloma (MM) for those with MM.

2.4. Comorbidities and co-medications

We used healthcare utilization records during a 365-day baseline period prior to the index date to assess the comorbidity and co-medication statuses. Chronic conditions that were highly prevalent among elderly patients were chronic gastritis/gastroesophageal reflux disease (GERD), chronic low back pain, and osteoarthritis [22]. We also assessed the underlying conditions reportedly associated with osteoarthritis (endocrine disorders, chronic obstructive pulmonary disease, rheumatologic and autoimmune diseases, depression, gastrointestinal disorders, end-stage renal disease, and hypogonadal states) and falling events (dementia, Parkinson's disease, epilepsy) [23]. Finally, we measured the Charlson Comorbidity Index (CCI), a weighted predictor of mortality, to assess the severity of morbidity status.

Medications known to affect osteoporosis such as bisphosphonates (zoledronic acid and pamidronate), proton pump inhibitors, selective serotonin reuptake inhibitors, anticonvulsants, glucocorticoids, thyroid hormones, and thiazolidinedione were included in the assessment [23]. All ICD-10 codes for comorbid conditions and Anatomical Therapeutic Chemical (ATC) codes for co-medication are presented in S1.

2.5. Definition of incidence

We estimated incidence by dividing the number of SREs by the sum of person-years and their 95% confidence intervals (CIs) [24]. We assessed person-years by following-up patients from the index date until the incident SRE. The incidences of initial SRE, including the first-ever SRE, and multiple SREs, including all recurrent SREs in each patient, were calculated. We compared the incidence rates according to the previous SRE history status in light of the finding of an increased risk of subsequent SREs after an initial SRE [4].

To estimate the incidence of multiple SREs, we measured the incidence both according to and irrespective of a 21-day time window. The 'with 21-day time window' classification indicated that the SRE event occurred at least 21 days after the previous SRE to be considered a subsequent SRE. Previous studies [24] have applied this definition of SRE incidence to ensure that interconnected events were not counted as distinct SREs. In addition, we assessed the cumulative incidence of SREs and the 95% CIs between 2004 and 2015 in total and by cancer type. The distributions of SREs were described according to the types of SREs. The ratio of the number of SREs during the follow-up period divided by the number of study subjects was defined as the cumulative incidence.

To observe whether the incidence differed according to baseline characteristics, we performed subgroup analyses based on the patient demographic information and comorbidity status regardless of SRE history. We measured the incidence rate ratio (IRR) to assess the relative differences in SRE incidence with respect to the 21-day time window.

2.6. Statistical analysis

Patient characteristics including age, sex, SRE history, comorbidities, co-medication, and CCI were summarized as counts with proportions for categorical variables and as means with standard deviations (SDs) for continuous variables. Chi-square tests were used to test for significant differences between cancer groups (BC, PC, and MM). In the subgroup analysis for the incidence of SREs, we estimated the incidence rate ratio (IRR) to compare the relative difference and the 95% CIs were assessed by calculating the standard deviation of the log rate ratio [25]. All data handling and statistical procedures were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

For the 12-year follow-up, we recruited our initial cohort of BC, PC, or MM patients (N = 386,921). Our final cohort comprised 53,231 patients (BC = 23,811; PC = 19,170; MM = 10,250) who had met our inclusion criteria, corresponding to 228,897 person-years (BC = 130,986; PC = 70,254; MM = 27,658). Table 1 describes the baseline characteristics of each cancer group. Most patients had no history of SREs (94.4%), which was calculated for one year prior to the index date. The highly prevalent comorbidities among the patients were chronic gastritis (59%), chronic back pain (35.9%), hypertension (33.5%), endocrine disorders (26.1%), osteoarthritis (25.6%), and rheumatologic and autoimmune diseases (24.2%). Glucocorticoid use was observed in 42.6% of patients, 14.9% of which used them for PPI. PC patients had the highest CCI score (mean: 3.37 ± 2.02), followed by BC (2.38 ± 1.64) and MM (1.02 ± 1.83) patients.

Table 2 describes the stratified incidence of SREs according to the history of previous SRE. Overall, patients with a previous history of SRE had higher SRE incidences than those in patients without an SRE history. The incidence of a first SRE was 0.31 (95% CI = 0.30–3.21) and 0.08 (95% CI = 0.08-0.08) for patients with a history of SRE and those without, respectively. The incidences of multiple SREs in patients with a previous history were 1.03 (95% CI = 1.01–1.05) using a 21-day time window and 3.53 (95% CI = 3.49–3.57) without the time window. The estimated incidences were 0.19 (95% CI = 0.19–0.20) and 1.12 (95% CI = 1.12–1.13), respectively, for patients without a history. Using the 21-day time window, MM patients with an SRE history had the highest SRE incidence of 1.44 (95% CI = 0.31-0.32), while those without had an incidence of 0.32 (95% CI = 0.31-0.32), followed by PC patients at 1.28 (95% CI = 1.23–1.34) and 0.18 (95% CI = 0.17–0.18) and BC patients at 0.57 (95% CI = 0.55–0.60) and 0.18 (95% CI = 0.18–0.18), respectively. The cumulative incidence of SREs during the study period was 39.7% in total, 47% in BC, 31.4% in PC, and 38.0% in MM (Table 3). The most common SRE was radiation in BC and PC and pathologic fracture in MM.

In the subgroup analyses, IRR showed a positive association with increasing age (IRR = 1.11, 95% CI = 1.07–1.14 in 40- to 64-year-olds; IRR = 1.32, 95% CI = 1.27–1.36 in 65- to 74-year-olds; and IRR = 1.68, 95% CI = 1.62–1.75 in 75-year-olds and over) (Table 4). BC and PC patients had lower IRRs compared to that in patients with MM (IRR = 0.41, 95% CI = 0.40-0.42 in BC; IRR = 0.44, 95% CI = 0.43-0.45 in PC).

4. Discussion

In this large population-based retrospective study of 53,231 patients diagnosed with MM or bone metastases from BC or PC, the incidence of multiple SREs with a 21-day time window ranged from 0.57 to 1.44 and from 0.18 to 0.32 in patients with and without a history of SREs, respectively. Furthermore, IRR increased with age and patients with chronic low back pain, osteoarthritis, and hypogonadal states were at a higher risk of experiencing a first SRE. The cumulative incidences of SREs during the 12-year follow-up were 47.0%, 31.4%, and 38.0% in BC, PC, and MM patients, respectively.

We defined our outcome of interest as multiple SREs with or without a 21-day time window as well as the incidence of a first SRE. It is meaningful to examine the incidence of multiple events since the risk of SREs increases after the first SRE [17]. Our results demonstrated incidences of multiple SREs of 2.74–5.18 without a 21-day time window for BC, PC, or MM patients with a history of SRE during the 12-year follow-up. A previous study analyzing multi-national prospective cohort data [13] reported patient-year adjusted rates of all SREs of 2.0–2.8 for Germany, 1.6–2.1 for Italy, 2.0–3.2 for Spain, and 2.4–3.9 for the UK among patients with a diagnosis of bone metastases secondary to solid tumor in the breast, lung, or prostate or multiple myeloma during the two-year study period. Hatoum et al. conducted a retrospective claims analysis in the US [8] and reported a monthly SRE rate of 0.43 ± 0.4 in patients with a history of SRE. The incidence rates in the European cohort were lower than our estimates; however, the European study had limited representativeness (631 patients).

Table 1
Baseline characteristics of patients with breast or prostate cancer-induced bone metastasis or multiple myeloma in the overall cohort selected from the National Health Insurance Database, 2004–2015.

Characteristics	Total		Breast cancer		Prostate cancer		Multiple myeloma	
	N	%	*N*	%	*N*	%	*N*	%
Age group (years)								
18–39	3,132	5.9	2,890	12.1	15	0.1	227	2.2
40–64	25,459	47.8	17,483	73.4	3,725	19.4	4,251	41.5
65–74	14,635	27.5	2,551	10.7	8,639	45.1	3,445	33.6
≥75	10,005	18.8	887	3.7	6,791	35.4	2,327	22.7
Sex								
Male	24,515	46.1	89	0.4	19,170	100.0	5,256	51.3
Female	28,716	53.9	23,722	99.6	0	0.0	4,994	48.7
History of SRE								
Yes	2,963	5.6	1,001	4.2	635	3.3	1,327	12.9
No	50,268	94.4	22,810	95.8	18,535	96.7	8,923	87.1
Comorbidities								
Chronic gastritis	31,429	59.0	13,574	57.0	14,548	75.9	3,307	32.3
Chronic low back pain	19,109	35.9	7,070	29.7	9,579	50.0	2,460	24.0
Osteoarthritis	13,608	25.6	4,699	19.7	7,115	37.1	1,794	17.5
Hypertension	17,848	33.5	5,094	21.4	10,430	54.4	2,324	22.7
Dementia	1,380	2.6	210	0.9	924	4.8	246	2.4
Parkinson's disease	359	0.7	83	0.3	226	1.2	50	0.5
Epilepsy	784	1.5	273	1.1	396	2.1	115	1.1
Endocrine disorders	13,904	26.1	5,397	22.7	6,756	35.2	1,751	17.1
COPD	7,501	14.1	13,904	58.4	3,878	20.2	983	9.6
Rheumatologic and autoimmune diseases	12,861	24.2	5,562	23.4	5,743	30.0	1,556	15.2
Depression	3,664	6.9	1,742	7.3	1,491	7.8	431	4.2
GI disorders	7,614	14.3	2,907	12.2	3,820	19.9	887	8.7
End-stage renal disease	179	0.3	30	0.1	47	0.2	102	1.0
Hypogonadal states	319	0.6	0	0.0	319	1.7	0	0.0
Co-medications								
Bisphosphonates	850	1.6	404	1.7	175	0.9	271	2.6
Glucocorticoids	22,680	42.6	10,631	44.6	9,582	50.0	2,467	24.1
Anticonvulsants	4,439	8.3	1,691	7.1	2,153	11.2	595	5.8
PPI	7,944	14.9	2,577	10.8	4,079	21.3	1,288	12.6
Thyroid hormones	877	1.6	608	2.6	129	0.7	140	1.4
SSRI	1,394	2.6	701	2.9	530	2.8	163	1.6
Thiazolidinediones	495	0.9	141	0.6	297	1.5	57	0.6
CCI (mean, SD)	(2.76, 1.91)		(2.38, 1.64)		(3.37, 2.02)		(1.02, 1.83)	
0	12,860	24.2	4,347	18.3	1,658	8.6	6,855	66.9
1	2,989	5.6	1,193	5.0	992	5.2	804	7.8
2	12,728	23.9	7,910	33.2	4,036	21.1	782	7.6
3	10,541	19.8	5,537	23.3	4,372	22.8	632	6.2
4	6,493	12.2	2,673	11.2	3,339	17.4	481	4.7
5+	7,620	14.3	2,151	9.0	4,773	24.9	696	6.8

Abbreviations: CCICharlson Comorbidity Index; SDstandard deviation; SREskeletal-related events; COPDchronic obstructive pulmonary disease; GI disordersgastrointestinal disorders; PPIproton pump inhibitors, SSRI, selective serotonin reuptake inhibitors.

Although it is difficult to directly compare the incidence rates from the US study to ours because of the different units, they do not appear to be very different.

In this study, the first SRE incidences were 0.31 (95% CI = 0.30–3.21) and 0.08 (95% CI = 0.08–0.08) for patients with a history of SRE and those without, respectively. A study conducted in Denmark using a nationwide database [11] reported an incidence of first SRE in bone metastases patients with BC of 0.58 (95% CI = 0.53–0.63) during a five-year follow-up. This result is higher than ours, which may be due to our long-term follow-up study design. According to Jensen et al., the first SRE occurred most frequently within the first year after the first diagnosis of bone metastasis, and the cumulative incidence converged toward a specific value five years after the bone metastasis [11]. Therefore, our 12-year long-term follow-up, resulting in a larger denominator, may have contributed to the relatively low incidence. Moreover, the Denmark study noted the possibility of overestimation in the risk of SREs due to inconsistencies in the recording of 'BC and SRE' and 'BC alone' in the registry database they utilized [11]. Since the Korea National Health Insurance Service database is used for reimbursement purposes by the Nationwide Health Insurance, differences in coding accuracy between BC and SRE are likely to be trivial, which may have also contributed to the discrepant results.

The cumulative SRE incidences were 47%, 31.4%, and 38.0% in BC, PC, and MM patients, respectively, which were generally similar to or slightly lower than those of previous reports in other countries [11,12]: three-year cumulative incidences of SRE of 48.9% and 57.2% in patients with bone metastasis from PC and BC, respectively, were reported in the US [12] and the five-year incidence was 51.7% among BC patients in Denmark [11]. Our findings may not be directly comparable to the estimated SRE incidence in previous observational studies owing to differences in racial or ethnic characteristics, healthcare setting, and data sources (claims database vs. chart reviews). Differences in the incidence of SREs between countries also can be explained by differences in disease management [26,27]. Cancer management, including surgery, radiation therapy, and systematic therapies, can prevent bone metastases or prolong the time to bone metastasis, and subsequently reduce the risk of SREs.

The risk of SRE tended to increase with increasing patient age, which may be linked to increased bone loss associated with aging due to various mechanisms [28–30]. The tendency was prominent in the multiple SRE analyses, suggesting that older patients may be more

Table 2
Incidence of skeletal-related events (SREs) with or without the application of a 21-day time window and stratified by SRE history in patients with breast or prostate cancer-induced bone metastasis or multiple myeloma, 2004-2015.

	Incidence of first SRE†			Multiple SREs‡					
				Without 21-day time window			With 21-day time window*		
	No. SREs‡	Person year	Incidence (95% CI)	No. SREs‡	Person year	Incidence (95% CI)	No. SREs‡	Person year	Incidence (95% CI)
Total									
Previous history of SRE	2,963	9,569	0.31 (0.30–3.21)	33,774	9,569	3.53 (3.49–3.57)	9,854	9,569	1.03 (1.01–1.05)
No previous history of SRE	18,153	219,328	0.08 (0.08–0.08)	246,309	219,328	1.12 (1.12–1.13)	42,343	219,328	0.19 (0.19–0.20)
Breast cancer									
Previous history of SRE	1,001	4,234	0.24 (0.22–0.25)	11,614	4,234	2.74 (2.69–2.79)	2,430	4,234	0.57 (0.55–0.60)
No previous history of SRE	10,201	126,752	0.08 (0.08–0.08)	144,813	126,752	1.14 (0.96–1.33)	22,684	126,752	0.18 (0.18–0.18
Prostate cancer									
Previous history of SRE	635	1,695	0.37 (0.35–0.41)	8,773	1,695	5.18 (5.07–5.29)	2,172	1,695	1.28 (1.23–1.34)
No previous history of SRE	5,387	68,559	0.08 (0.08–0.08)	77,136	68,559	1.13 (1.12–1.13)	12,069	68,559	0.18 (0.17–0.18)
Multiple myeloma									
Previous history of SRE	1,327	3,641	0.36 (0.35–0.38)	13,387	3,641	3.68 (3.62–3.74)	5,252	3,641	1.44 (1.40–1.48)
No previous history of SRE	2,565	24,017	0.11 (0.10–0.11)	24,360	24,017	1.01 (1.00–1.03)	7,590	24,017	0.32 (0.31–0.32)

Abbreviations: CI, confidence interval. † Initial SRE after the index date was used. ‡ Multiple counts of all recurrent SREs for each patient. * The event must have occurred at least 21 days apart from the previous SRE to be considered a subsequent SRE.

Table 3
Cumulative incidence of skeletal-related events (SREs) in patients with breast or prostate cancer induced bone metastasis or multiple myeloma, 2004-2015.

	No. of patients with SRE	Cumulative incidence†	95% CI
Total (*N* = 53,231)			
Total	21,116	39.7%	(39.3–40.1)
Pathologic fracture	6,684	12.6%	(12.3–12.9)
Spinal cord compression	1,345	2.5%	(2.4–2.6)
Radiation	15,234	28.6%	(28.2–29.0)
Surgery to bone	3,904	7.3%	(7.1–7.5)
Breast cancer (*N* = 23,811)			
Total	11,202	47.0%	(46.4–47.6)
Pathologic fracture	2,260	9.5%	(9.1–9.9)
Spinal cord compression	341	1.4%	(1.3–1.6)
Radiation	9,434	39.6%	(39.0–40.2)
Surgery to bone	1,558	6.5%	(6.2–6.8)
Prostate cancer (*N* = 19,170)			
Total	6,022	31.4%	(30.7–32.0)
Pathologic fracture	2,032	10.6%	(10.2–11.0)
Spinal cord compression	467	2.4%	(2.2–2.6)
Radiation	3,967	20.7%	(20.1–21.3)
Surgery to bone	1,320	6.9%	(6.5–7.3)
Multiple myeloma (*N* = 10,250)			
Total	3,892	38.0%	(37.1–38.9)
Pathologic fracture	2,392	23.3%	(22.5–24.1)
Spinal cord compression	537	5.2%	(4.8–5.6)
Radiation	1,833	17.9%	(17.2–18.6)
Surgery to bone	1,026	10.0%	(9.4–10.6)

Abbreviations: CI, confidence interval.
† Cumulative incidence = (No. of patients with SRE/total number of study subjects); 95% CI calculated.

vulnerable to subsequent SREs. Some comorbid conditions were also likely to be associated with the risk of SREs. Patients with rheumatologic and autoimmune diseases, chronic low back pain, osteoarthritis, chronic gastritis, epilepsy, hypogonadal states, or glucocorticoid use had higher IRRs compared to those in patients who did not have these conditions. Given that hypogonadism or chronic gastritis has been reported to decrease calcium absorption and bone formation [31,32], it could be expected to act as a risk factor for SRE. Rheumatologic and autoimmune diseases may result in severe joint and bone loss by attacking normal cells and tissues around the joints. Epilepsy may be associated with an increased risk of fall and consequent SREs. Therefore, patients at risk for SREs; i.e., those with older age and comorbidities associated with bone loss, require vigilant surveillance and prevention strategies.

The present study used a nationwide, real-world database to estimate the incidence of SREs. To our knowledge, the only two studies that have investigated the incidence of SREs in routine clinical practice were conducted in Denmark and the US and there is no previous Asian population-based cohort study on the incidence of SREs. Furthermore, data on the differences in SRE rates after bone metastasis or MM according to SRE history are scarce even though a previous history of SRE is a known risk factor of SRE [33,34]. We calculated the incidence of initial and multiple SREs according to SRE history and patient characteristics. Moreover, we identified the real-world incidence of SRE in MM patients. As the incidence of MM was relatively lower than that of other types of cancer, it could be difficult to investigate the sufficient number of MM patients in previous studies.

This study has limitations inherent to observational studies using electronic claims data. First, potential inaccuracies in diagnosis coding and incomplete records could have undermined the validity of our findings. The outcome was determined based on the various diagnosis and procedure codes related to SREs; thus, outcomes not recorded may have been overlooked, leading to a falsely lower incidence. Second, the results could be biased by outcome misclassification. Since numerous diagnosis and procedure codes were utilized to define SREs, there is a greater chance of including misclassified outcomes compared to the use of a simple outcome definition. Although a previous validation study comparing the diagnosis codes from the health insurance database with the actual diagnoses in patients' medical records in South Korea reported an overall positive predictive value of diagnoses of about 82% [35], additional studies are necessary to examine the validity of SRE codes. Third, there may be undetected effects of cancer management, including surgery, radiation therapy, and systematic therapies, which may prevent bone metastases, and subsequently reduce the risk of SREs.

In conclusion, this large, population-based study provided real-world evidence that patients with BC- or PC-induced bone metastasis or MM are at high risk of SREs. These findings may facilitate enhanced understanding of SREs among healthcare professionals and provide useful information for these patients. The incidence of multiple SREs in this South Korean cohort was higher than those in European populations. Further multi-national studies are recommended to evaluate SRE incidence and the effect of cancer management to assess differences according to disease management, ethnicities, or healthcare systems.

Table 4
Subgroup analyses of the incidence of skeletal-related events (SREs) with the initial SRE and multiple SREs with the 21-day time window in patients with breast or prostate cancer-induced bone metastasis or multiple myeloma, 2004–2015.

			Incidence of first SRE†			Multiple SREs‡		
	No. of patients	Sum of person-years	No. of first SRE	IR	IRR (95% CI)	No. of multiple SREs	IR	IRR (95% CI)
Age group (years)								
≤ 39	3,132	19,305	1,744	0.09	Ref	3,736	0.19	Ref
40-64	25,459	129,587	11,347	0.09	0.97 (0.92–1.02)	26,928	0.21	1.11 (1.07–1.14)
65-74	14,635	54,787	5,096	0.09	1.03 (0.98–1.09)	13,502	0.25	1.32 (1.27–1.36)
≥ 75	10,005	25,218	2,929	0.12	1.29 (1.21–1.36)	8,031	0.32	1.68 (1.62–1.75)
Gender								
Male	24,515	84,531	7,899	0.09	Ref	19,802	0.23	Ref
Female	28,716	144,366	13,217	0.09	1.02 (0.99–1.05)	32,395	0.22	0.96 (0.94–0.97)
Cancer type								
MM	10,250	27,658	3,892	0.14	Ref	12,842	0.46	Ref
BC	23,811	130,986	11,202	0.09	0.61 (0.59–0.63)	25,114	0.19	0.41 (0.40–0.42)
PC	19,170	70,254	6,022	0.09	0.61 (0.59–0.63)	14,241	0.20	0.44 (0.43–0.45)
CCI								
0	12,860	51,939	6,262	0.12	Ref	19,020	0.37	Ref
1	2,989	15,142	1,264	0.08	0.69 (0.65–0.74)	3,162	0.21	0.57 (0.55–0.59)
2	12,728	61,112	5,136	0.08	0.70 (0.67–0.72)	11,083	0.18	0.49 (0.48–0.50)
3	10,541	47,745	3,904	0.08	0.68 (0.65–0.71)	8,586	0.18	0.49 (0.47–0.50)
4	6,493	26,922	2,188	0.08	0.67 (0.64–0.71)	4,957	0.18	0.49 (0.47–0.50)
5+	7,620	26,038	2,362	0.09	0.75 (0.72–0.79)	5,389	0.21	0.57 (0.55–0.58)

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; MM, multiple myeloma; BC, breast cancer; PC, prostate cancer. † Initial SRE after the index date was used. ‡ Multiple counts of SREs: the event must have occurred at least 21 days apart from the previous SRE to be considered a subsequent SRE.

Authorship contribution statement

YHB, HLJ, and ISO designed the study, performed the statistical analyses, and interpreted the data. YHB and HLJ wrote the manuscript. YHB revised the manuscript. HY and JP interpreted the data and critically revised the manuscript. JYS designed the study, supervised the statistical analyses and the interpretation of data, and critically revised the manuscript.

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Conflict of interest statement

This study was supported by Amgen Inc. JYS received grant support to her institutions from Amgen. HY and JP are full-time employees of Amgen Limited Korea. However, the authors had full control of the findings and the results presented without any supervision or interference from the sponsors of the work.

Data statement

Our study used a population-based nationwide health insurance claims database established by the National Health Insurance Service (NHIS) of South Korea. NHIS forbids the transfer, rent, or sale of the database to any third party other than the researcher, who obtained the approval for the provided database (Website of NHIS: https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do; Contact information of data access committee: +82-33-736-2430).

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References

[1] G.D. Roodman, Mechanisms of bone metastasis, N. Engl. J. Med. 350 (2004) 1655–1664.
[2] L.J. Suva, R.J. Griffin, I. Makhoul, Mechanisms of bone metastases of breast cancer, Endocr. Relat. Cancer 16 (2009) 703–713.
[3] Y. Kang, P.M. Siegel, W. Shu, M. Drobnjak, S.M. Kakonen, C. Cordón-Cardo, et al., A multigenic program mediating breast cancer metastasis to bone, Cancer Cell 3 (2003) 537–549.
[4] M. Clemons, K.A. Gelmon, K.I. Pritchard, A.H. Paterson, Bone-targeted agents and skeletal-related events in breast cancer patients with bone metastases: the state of the art, Curr. Oncol. 19 (2012) 259–268.
[5] M.R. Smith, F. Saad, R. Coleman, N. Shore, K. Fizazi, B. Tombal, et al., Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial, Lancet 379 (2012) 39–46.
[6] A. Ibrahim, N. Scher, G. Williams, R. Sridhara, N. Li, G. Chen, et al., Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases, Clin. Cancer. Res. 9 (2003) 2394–2399.
[7] A. Lipton, Pathophysiology of bone metastases: how this knowledge may lead to therapeutic intervention, J. Support. Oncol. 2 (2004) 205–213 discussion 213–214, 216–217, 219–220.
[8] H.T. Hatoum, S.J. Lin, M.R. Smith, V. Barghout, A. Lipton, Zoledronic acid and skeletal complications in patients with solid tumors and bone metastases: analysis of a national medical claims database, Cancer 113 (2008) 1438–1445.
[9] N. Sathiakumar, E. Delzell, M.A. Morrisey, C. Falkson, M. Yong, V. Chia, et al., Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US medicare beneficiaries, 1999-2006, Prostate Cancer Prostatic Dis. 14 (2011) 177–183.
[10] N. Sathiakumar, E. Delzell, M.A. Morrisey, C. Falkson, M. Yong, V. Chia, et al., Mortality following bone metastasis and skeletal-related events among women with breast cancer: a population-based analysis of U.S. medicare beneficiaries, 1999-2006, Breast Cancer Res. Treat. 131 (2012) 231–238.
[11] A.O. Jensen, J.B. Jacobsen, M. Nørgaard, J.P. Fryzek, H.T. Sørensen, Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark, BMC Cancer 11 (2011) 29.
[12] G. Oster, L. Lamerato, A.G. Glass, K.E. Richert-Boe, A. Lopez, K. Chung, et al., Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems, Support Care Cancer 21 (2013) 3279–3286.
[13] G. Hechmati, S. Cure, A. Gouepo, H. Hoefeler, V. Lorusso, D. Lüftner, et al., Cost of skeletal-related events in European patients with solid tumours and bone metastases: data from a prospective multinational observational study, J. Med. Econ. 16 (2013) 691–700.
[14] D.J. Dinter, W.K. Neff, J. Klaus, C. Böhm, J. Hastka, C. Weiss, et al., Comparison of whole-body MR imaging and conventional X-ray examination in patients with multiple myeloma and implications for therapy, Ann. Hematol. 88 (2009) 457–464.
[15] M.E. Mulligan, A.Z. Badros, PET/CT and MR imaging in myeloma, Skeletal Radiol. 36 (2007) 5–16.
[16] R.E. Coleman, Metastatic bone disease: clinical features, pathophysiology and

treatment strategies, Cancer Treat. Rev. 27 (2001) 165–176.
[17] F. Saad, D.M. Gleason, R. Murray, S. Tchekmedyian, P. Venner, L. Lacombe, et al., Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer, J. Natl. Cancer Inst. 96 (2004) 879–882.
[18] S. Kwon, Payment system reform for health care providers in Korea, Health Policy Plan. 18 (2003) 84–92.
[19] K. Fizazi, A. Lipton, X. Mariette, J.J. Body, Y. Rahim, J.R. Gralow, et al., Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates, J. Clin. Oncol. 27 (2009) 1564–1571.
[20] G.J. Morgan, F.E. Davies, W.M. Gregory, A.J. Szubert, S.E. Bell, M.T. Drayson, et al., Effects of induction and maintenance plus long-term bisphosphonates on bone disease in patients with multiple myeloma: the medical research council myeloma IX trial, Blood 119 (2012) 5374–5383.
[21] M.L. Svendsen, H. Gammelager, C. Svaerke, M. Yong, V.M. Chia, C.F. Christiansen, et al., Hospital visits among women with skeletal-related events secondary to breast cancer and bone metastases: a nationwide population-based cohort study in Denmark, Clin. Epidemiol. 5 (2013) 97–103.
[22] H.A. Kim, J.Y. Shin, M.H. Kim, B.J. Park, Prevalence and predictors of polypharmacy among Korean elderly, PLoS One 9 (2014) e98043.
[23] National Osteoporosis Foundation: 2013, Clinician's Guide to Prevention and Treatment of Osteoporosis, National Osteoporosis Foundation, Washington, DC, 2013 (Accessed 1 May 2018), https://www.nof.org/news/nofs-clinicians-guide-published-by-osteoporosis-international/.
[24] K. Fizazi, M. Carducci, M. Smith, R. Damião, J. Brown, L. Karsh, et al., Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study, Lancet 377 (2011) 813–822.
[25] K.J. Rothman, S. Greenland, T. Lash, Modern Epidemiology, third ed, Lippincott Williams & Wilkins, Philadelphia, 2008.
[26] R.J. Van Ewijk, L. Schwentner, A. Wöckel, J. König, R. Kreienberg, M. Blettner, et al., Trends in patient characteristics, treatment and survival in breast cancer in a non-selected retrospective clinical cohort study of 2,600 patients, Arch. Gynecol. Obstet. 287 (2013) 103–110.
[27] S.S. Mougalian, P.R. Soulos, B.K. Killelea, D.R. Lannin, M.M. Abu-Khalaf, M.P. DiGiovanna, et al., Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States, Cancer 121 (2015) 2544–2552.
[28] P.D. Delmas, D. Stenner, H.W. Wahner, K.G. Mann, B.L. Riggs, Increase in serum bone gamma-carboxyglutamic acid protein with aging in women. Implications for the mechanism of age-related bone loss, J. Clin. Invest. 71 (1983) 1316–1321.
[29] G.A. Ledger, M.F. Burritt, P.C. Kao, W.M. O'Fallon, B.L. Riggs, S. Khosla, Role of parathyroid hormone in mediating nocturnal and age-related increases in bone resorption, J. Clin. Endocrinol. Metab. 80 (1995) 3304–3310.
[30] H.M. Frost, On our age-related bone loss: insights from a new paradigm, J. Bone. Miner. Res. 12 (1997) 1539–1546.
[31] R.M. Francis, M. Peacock, J.E. Aaron, P.L. Selby, G.A. Taylor, J. Thompson, et al., Osteoporosis in hypogonadal men: role of decreased plasma 1,25-dihydroxyvitamin D, calcium malabsorption, and low bone formation, Bone 7 (1986) 261–268.
[32] N. Mauras, V.Y. Hayes, N.E. Vieira, A.L. Yergey, K.O. O'Brien, Profound hypogonadism has significant negative effects on calcium balance in males: a calcium kinetic study, J. Bone. Miner. Res. 14 (1999) 577–582.
[33] J.E. Brown, R.J. Cook, A. Lipton, L. Costa, R.E. Coleman, Prognostic factors for skeletal complications from metastatic bone disease in breast cancer, Breast Cancer Res. Treat. 123 (2019) 767–779.
[34] R. Tanaka, K. Yonemori, A. Hirakawa, F. Kinoshita, N. Takahashi, J. Hashimoto, et al., Risk factors for developing skeletal-related events in breast cancer patients with bone metastases undergoing treatment with bone-modifying agents, Oncologist 21 (2016) 508–513.
[35] E.C. Park, S.I. Jang, S.Y. Jeon, S.A. Lee, J.E. Lee, D.W. Choi, Report of the Evaluation for Validity of Discharged Diagnoses in Korean Health Insurance Database, (2017).