ORIGINAL RESEARCH

Estimated number of prevalent cases of metastatic bone disease in the US adult population

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Background: The prevalence of metastatic bone disease in the US population is not well understood. We sought to estimate the current number of US adults with metastatic bone disease using two large administrative data sets.

Methods: Prevalence was estimated from a commercially insured cohort (ages 18–64 years, MarketScan database) and from a fee-for-service Medicare cohort (ages ≥65 years, Medicare 5% database) with coverage on December 31, 2008, representing approximately two-thirds of the US population in each age group. We searched for claims-based evidence of metastatic bone disease from January 1, 2004, using a combination of relevant diagnosis and treatment codes. The number of cases in the US adult population was extrapolated from age- and sex-specific prevalence estimated in these cohorts. Results are presented for all cancers combined and separately for primary breast, prostate, and lung cancer.

Results: In the commercially insured cohort (mean age = 42.3 years [SD = 13.1]), we identified 9505 patients (0.052%) with metastatic bone disease. Breast cancer was the most common primary tumor type (n = 4041). In the Medicare cohort (mean age = 75.6 years [SD = 7.8]), we identified 6427 (0.495%) patients with metastatic bone disease. Breast (n = 1798) and prostate (n = 1862) cancers were the most common primary tumor types. We estimate that 279,679 (95% confidence interval: 274,579–284,780) US adults alive on December 31, 2008, had evidence of metastatic bone disease in the previous 5 years. Breast, prostate, and lung cancers accounted for 68% of these cases.

Conclusion: Our findings suggest that approximately 280,000 US adults were living with metastatic bone disease on December 31, 2008. This likely underestimates the true frequency; not all cases of metastatic bone disease are diagnosed, and some diagnosed cases might lack documentation in claims data.

Keywords: bone neoplasms, epidemiology, metastasis, prevalence

Introduction

Bone is a common site of metastatic cancer.[1,2] Bone metastases occur in most tumor types but are most prevalent in cancers of the breast, prostate, and lung.[3] These bone lesions can cause serious skeletal complications, including spinal cord or nerve root compression, bone surgery, hypercalcemia of malignancy, pathologic fractures, and severe bone pain requiring palliative radiotherapy,[4,5] all of which can significantly compromise quality of life[6–10] and may negatively affect survival.[11,12] Palliation of pain, prevention of skeletal complications, and maintenance of quality of life are the primary objectives in managing patients with metastatic bone disease.[5]

A diagnosis of malignant bone disease generally represents an incurable cancer. However, the clinical course can be prolonged. Based on recent research using

population-based and medical registries in Denmark, 1- and 3-year cumulative survival in breast cancer patients diagnosed with bone metastases was 59% and approximately 22%,[13] respectively. Similarly, 1- and 3-year cumulative survival in prostate cancer patients diagnosed with bone metastases was 47% and approximately 9%,[14] respectively. These data demonstrate that for some patients, metastatic bone disease is a chronic condition that must be carefully managed.

To better understand the burden of metastatic bone disease in the United States, current and reliable estimates of prevalent cases are important. Estimates of incidence rates and subsequent survival in a population-based setting are available,[13–17] but current prevalence data are scant. We sought to estimate the current number of patients with metastatic bone disease in the US adult population by applying a claims-based definition of metastatic bone disease to two large administrative data sets.

Methods
Data sources and study participants
Two data sources were used in this analysis: the MarketScan database and the Medicare 5% database. MarketScan is a large commercial claims and encounters database of specific health services records, demographics, and enrollment information for employees and their dependants selected from employer health insurance plans. It includes information on diagnoses, procedures performed and reimbursed by commercial insurance, and dates of service.

The Medicare 5% database is a random sample of all Medicare beneficiaries. It includes the annual denominator file, which contains information on demographics and enrollment in Medicare and managed care organizations (health maintenance organizations [HMO]) for each beneficiary; and the annual claims-based Standard Analytic Files, which contain Part A institutional and Part B physician/suppliers files. Claims-based files include information on diagnoses, procedures performed and reimbursed by Medicare, and dates of service.

Two point-prevalent study cohorts were assembled of beneficiaries with insurance coverage on December 31, 2008. The first included employees and their dependants enrolled in fee-for-service plans through their employers and aged 18–64 years on December 31, 2008 ("commercially insured" cohort). The second included Medicare Parts A and B beneficiaries not enrolled in HMOs ("fee-for-service Medicare" cohort), residing in the 50 states and District of Columbia and aged ≥65 years on December 31, 2008. We examined

all available claims for each cohort member in the preceding 5 years (January 1, 2004, through December 31, 2008) for evidence of metastatic bone disease.

Identification of metastatic bone disease, cancer, and cancer type
Patients were identified as having metastatic bone disease by (1) at least one inpatient claim or two outpatient claims on different days within any 12-month interval, carrying the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for secondary malignant neoplasm of bone or bone marrow (198.5); or (2) at least one claim carrying Healthcare Common Procedure Coding System codes for intravenous (IV) bisphosphonates zoledronic acid (Zometa, J3487) or pamidronate (J2430) with at least one qualifying code on the same claim. Qualifying codes included the ICD-9-CM diagnosis codes for primary cancer (see Table 1); metastatic cancer in lymph nodes (196.xx), respiratory and digestive systems (197.xx), and other sites including bone and bone marrow (198.xx); and V codes for encounters for antineoplastic chemotherapy (V58.11) and immunotherapy (V58.12). The earliest date of

Table 1 International Classification of Diseases, Ninth Edition, Clinical Modification diagnosis codes used to identify cancer types

Cancer types	Diagnosis codes
Head and neck	140-14999
Esophagus	150-15099
Stomach and small intestine	151-15299
Colon and rectum	153-15489
Liver	155-15529
Gallbladder	156-15699
Pancreas	157-15799
Retroperitoneum and peritoneum	158-15899
Spleen	159-15999
Lung	162-16399
Other respiratory	160-16199, 164-16599
Bone	170-17099
Connective and soft tissue	171-17199
Melanoma	172-17299
Female breast	174-17499
Male breast	1750 or 1759
Sarcoma	176-17699
Gynecologic	179-18499
Prostate	185
Other genitourinary	186-18999
Central nervous system	190-19299
Endocrine	193-19499
Non-Hodgkin's lymphoma	200-20099, 202-20299
Hodgkin's lymphoma	201-20199
Multiple myeloma	203-20380
Leukemia	204-20891
Ill-defined	195-19599, 199-19999

bone metastasis code or qualifying IV bisphosphonate code was defined as the bone metastasis index date.

These patients were also required to have claims-based evidence of primary cancer during a 12-month interval from 6 months before to 6 months after the bone metastasis index date. Cancer type was defined by presence of the ICD-9-CM diagnosis code for a specific cancer type (Table 1) on at least one inpatient claim or two outpatient claims on different days in the 12-month interval. We included multiple myeloma and primary bone malignancies in our study because, while we recognize that these are intrinsic diseases of the bone, any malignancies with invasion of bone (bone metastases from solid tumors, multiple myeloma, etc) share substantial clinical consequences and may be indicated for and benefit from similar management. Further, we wanted our analysis to be consistent with other reports of the burden of metastatic bone disease[18] for comparison purposes. Solid tumors that most frequently metastasize to bone (breast cancer [female only], prostate cancer, and lung cancer) were of interest in this study. When there was claims-based evidence of more than one of these three cancer types, the following algorithm was applied to identify a single type: (1) if there were bisphosphonate claims, the cancer type coded most frequently on these claims was chosen; (2) if there were no bisphosphonate claims, the cancer type coded most frequently on all claims during the 12-month interval was chosen.

Estimation of number of prevalent cases in the national commercially insured population and fee-for-service Medicare population

The number of prevalent cases of metastatic bone disease in the national commercially insured population aged 18–64 years was extrapolated with person-level weights derived from the Medical Expenditure Panel Survey and provided by the data vendor.[19] The number of prevalent cases in the national fee-for-service Medicare population aged ≥65 years was extrapolated by multiplying observed estimates in the 5% sample by twenty.

Estimation of the number of prevalent cases in the US adult population

To account for US citizens not represented in the commercially insured or the Medicare populations, the number of prevalent cases estimated in these two data sources was extrapolated to the entire US adult population by applying age- and sex-specific prevalence estimates to the 2008 US Census population.[20] Age- and sex-specific prevalence estimates were produced by extrapolating the observed estimates for each age (18–44, 45–64, 65–74, 75–84, and ≥85 years) and sex combination to the commercially insured population aged 18–64 years and the fee-for-service Medicare population aged ≥65 years. Multiplying the age- and sex-specific prevalence estimates by counts of US populations in each category produced the total number of cases in each category. Summing these age- and sex-specific cases produced an estimated total number of patients living with metastatic bone disease in the US adult population as of December 31, 2008. This analysis was conducted for all cancers combined and then repeated for breast, prostate, and lung cancers.

All analyses were conducted using SAS software (version 9.1; SAS Institute Inc, Cary, NC).

Results

Demographic characteristics

The commercially insured cohort included 18,218,583 enrollees who met the inclusion criteria; 52.4% were aged 18–44 years and 47.7% were men. The fee-for-service Medicare cohort included 1,297,538 beneficiaries who met the inclusion criteria; 50.6% were aged 65–74 years, 34.5% were aged 75–84 years, and 42.2% were men.

Number of patients with metastatic bone disease in the study cohorts

Table 2 presents the number of patients meeting the case definition for metastatic bone disease and the distribution of case definition sources in each study cohort. In the commercially insured cohort, we identified 9505 patients (0.052% of the cohort) living with metastatic bone disease on December 31, 2008. Of the solid tumors examined separately, breast cancer was the most common primary tumor type (n = 4041). In the Medicare cohort, we identified 6427 (0.495%) patients with metastatic bone disease. Breast (n = 1798) and prostate (n = 1862) cancers were the most common primary tumor types.

Compared with elderly patients, younger patients with metastatic bone disease were more often identified from drug codes only (commercially insured: 27.9%, Medicare: 20.1%), less frequently identified from the diagnosis codes only (commercially insured: 28.9%, Medicare: 37.0%), and about equally as often identified from both drug and diagnosis codes (commercially insured: 43.3%, Medicare: 43.0%). Case definition sources varied considerably across the three

Table 2 Number of patients meeting the metastatic bone disease case definition in the commercially insured and Medicare 5% sample cohorts and case definition sources, all cancers and by specific cancer types

Cancer type	Commercially insured cohort (n = 18,218,583)				Medicare 5% sample cohort (n = 1,297,538)			
	n (%)	Definition sources[a]			n (%)	Definition sources[a]		
		Diagnosis codes only	Drug codes only	Both		Diagnosis codes only	Drug codes only	Both
All cancers	9505 (0.052)	28.9	27.9	43.3	6427 (0.495)	37.0	20.1	43.0
Female breast	4041 (0.022)	17.6	23.9	58.5	1798 (0.139)	27.2	18.5	54.3
Prostate	776 (0.004)	31.6	15.7	52.7	1862 (0.144)	40.3	11.9	47.8
Lung	1253 (0.007)	49.2	10.2	40.6	795 (0.061)	57.5	6.9	35.6
Other	3435 (0.019)	34.1	41.7	24.3	1972 (0.152)	34.5	34.5	31.0

Note: [a]Percent of row total.

cancer types of interest; the proportion of cases identified by diagnosis code alone was highest for lung cancer and lowest for breast cancer.

Estimated number of prevalent cases of metastatic bone disease in the national commercially insured population and fee-for-service Medicare population

By applying the person-level weights, we estimated a total of 60,411 (95% confidence interval [CI]: 59,134–61,689) patients living with metastatic bone disease on December 31, 2008, among 120.7 million commercially insured persons aged 18–64 years in the United States; patients with breast, prostate, or lung cancer accounted for 64% of prevalent cases of metastatic bone disease. Among the 26 million fee-for-service Medicare enrollees in the United States, 128,540 (95% CI: 125,485–131,595) patients were living with metastatic bone disease; 69% of cases occurred in patients with the specified cancer types. Table 3 presents estimates of prevalent cases of metastatic bone disease in these two large components of the insured US adult population for all cancers and by the three specific types of interest.

Estimated number of prevalent cases of metastatic bone disease in the US adult population

Table 3 also presents estimates of prevalent cases of metastatic bone disease for the entire US adult population based on the age- and sex-specific prevalence estimates as shown in Table 4. We estimated that a total of 279,679 (95% CI: 274,579–284,780) US adults alive on December 31, 2008, had evidence of metastatic bone disease in the previous 5 years. Of the three cancer types examined separately, female breast cancer was the most common primary cancer type, accounting for about one-third of total metastatic bone disease cases in the US adult population (n = 90,904; 95% CI: 88,095–93,714). Prostate cancer was the second most common (n = 62,841; 95% CI: 60,253–65,429), and lung cancer was the least common of the specific cancer types examined (n = 35,222; 95% CI: 33,415–37,030). These three cancer types combined accounted for 68% of total metastatic bone disease cases.

Discussion

This descriptive study estimated the number of point-prevalent cases of metastatic bone disease in the US adult

Table 3 Estimated number of prevalent cases of metastatic bone disease in the national commercially insured population aged 18–64 years, the national fee-for-service Medicare population aged ≥65 years, and the US adult population on December 31, 2008, all cancers and by specific cancer types

Cancer type	Commercially insured, ages 18–64 years (n = 120,694,145)	Fee-for-service Medicare, ages ≥65 years (n = 25,950,760)	US adult population[a] (n = 230,118,000)
All cancers	60,411 (59,134–61,689)	128,540 (125,485–131,595)	279,679 (274,579–284,780)
Female breast	25,754 (24,911–26,596)	35,960 (34,341–37,579)	90,904 (88,095–93,714)
Prostate	4,969 (4,609–5,329)	37,240 (35,593–38,887)	62,841 (60,253–65,429)
Lung	7,879 (7,421–8,337)	15,900 (14,823–16,977)	35,222 (33,415–37,030)
Other	21,809 (21,046–22,573)	39,440 (37,745–41,135)	90,712 (87,843–93,580)

Notes: Data presented as estimated number of patients with metastatic bone disease (95% confidence interval). [a]US Census 2008.

Table 4 Age- and sex-specific prevalence estimates of metastatic bone disease and distribution of age and sex in the US adult population

Sex	Age, years	Insured population,[a] n	Prevalence of metastatic bone disease (standard error), per 10,000 population					US population,[b] n
			All cancers	Female breast	Prostate	Lung	Other	
Men	18–44	32,978,252	0.64 (0.04)		0.03 (0.01)	0.09 (0.02)	0.52 (0.04)	57,522,000
	45–64	26,686,875	6.96 (0.14)		1.82 (0.07)	1.35 (0.06)	3.79 (0.11)	38,104,000
	65–74	6,043,760	41.99 (1.18)		19.33 (0.80)	7.05 (0.48)	15.62 (0.72)	9,265,000
	75–84	3,686,380	73.41 (1.99)		45.74 (1.57)	8.30 (0.67)	19.37 (1.02)	5,336,000
	≥85	1,210,060	90.74 (3.86)		71.90 (3.43)	4.30 (0.84)	14.54 (1.55)	1,864,000
Women	18–44	32,729,023	1.41 (0.06)	0.99 (0.05)		0.10 (0.02)	0.33 (0.03)	55,666,000
	45–64	28,299,994	12.40 (0.19)	7.96 (0.15)		1.29 (0.06)	3.15 (0.10)	39,956,000
	65–74	7,076,540	40.39 (1.07)	22.53 (0.80)		6.25 (0.42)	11.62 (0.57)	10,858,000
	75–84	5,269,160	50.63 (1.38)	27.40 (1.02)		5.43 (0.45)	17.80 (0.82)	7,689,000
	≥85	2,664,860	37.00 (1.66)	20.94 (1.25)		2.93 (0.47)	13.13 (0.99)	3,858,000

Notes: [a]National commercially insured population aged 18–64 years and fee-for-service Medicare population aged ≥65 years; [b]US Census 2008.

population on December 31, 2008, using a large commercial insurance claims database and the Medicare 5% sample database. Our findings suggest that approximately 280,000 US adults were living with metastatic bone disease on December 31, 2008, with 68% of cases occurring in patients with primary breast, prostate, or lung cancer.

To our knowledge, Schulman and Kohles[18] published the only other study aimed at describing the burden of metastatic bone disease in the US population in terms of prevalence. The similar magnitude of our national point-prevalence estimate (279,679) and the Schulman and Kohles[18] period-prevalence estimate of the size of the US population with metastatic bone disease between 2000–2004 (256,137) obscures important differences in numbers by cancer type. Compared with their estimates, ours were 30% higher for breast cancer, 32% higher for prostate cancer, 5% lower for lung cancer, and 11% lower for all other cancer types combined. The study methodologies differ in important ways beyond estimation of point- versus period-prevalence. Schulman and Kohles[18] included pediatric patients (though few cases were identified) and used prevalence estimates for Medicare enrollees with supplemental employer-paid insurance to extrapolate to the full Medicare population. How well this Medicare subset represents the entire Medicare population is debatable. We limited our extrapolation to the Medicare fee-for-service population, having studied a random sample of this population in the Medicare 5% data set. Rather than make the assumption that the overall prevalence of metastatic bone disease in the population not covered by commercial insurance or by Medicare was the same as in the commercially insured or Medicare population, we took the approach of calculating observed age- and sex-specific prevalence, based on our extrapolation to the commercially insured (ages 18–64 years)

and fee-for-service Medicare (aged ≥65 years) populations, and applied these estimates to counts of the US adult population in each stratum from the US Census.

Another key difference is that we included bisphosphonate treatment in the case definition of bone metastasis. Schulman and Kohles[18] identified patients with the first documented diagnosis of primary cancer, and followed claims over time for evidence of metastatic bone disease defined by at least one ICD-9-CM code for metastatic bone disease (198.5) or by a primary diagnosis code for a cancer type other than bone cancer and a secondary diagnosis code for bone cancer (170.xx). We assessed whether cohort members met a claims-based definition for metastatic bone disease before identifying cancer type. Our case definition required one inpatient claim with an ICD-9-CM code of 198.5 or two outpatient claims with this code on different days within any 1-year interval between 2004–2008 (to avoid including patients who were tested to rule out metastatic bone disease and had no further claims evidence of metastatic bone disease). We also included in the case definition one or more claims for IV zoledronic acid (Zometa) or pamidronate, provided the claim included a code for cancer or cancer treatment. The only licensed indications for these two therapies in cancer patients are bone lesions from solid tumors or multiple myeloma and hypercalcemia of malignancy, which is relatively rare and even rarer in the absence of bone metastasis.[21] Our decision to include bisphosphonate treatment in the case definition was motivated by concern that use of diagnosis codes alone to identify metastatic bone disease results in relatively low sensitivity.[22]

The strength of this study is that the data sets used included representative samples of two large components of the US adult population. The commercial claims database is

one of the larger in the US and contains data on approximately 24 million employees and their dependants aged younger than 65 years who have health insurance through their employers. Approximately 18 million individuals were included in our study. Weights contained in this database allowed us to project estimates of bone metastasis prevalence to approximately 121 million US adults aged 18–64 years covered by employer-sponsored insurance, representing 63% of the total US population of this age range. The Medicare 5% sample database is essentially a random sample of approximately 44 million Medicare beneficiaries. Estimates from approximately 1.3 million individuals eligible for our study were projected to 26 million Medicare fee-for-service enrollees with Part A and Part B coverage, accounting for two-thirds of the US population aged ≥65 years. Furthermore, age and sex distribution in the two projected populations were similar to the total US adult population aged 18–64 and ≥65 years, respectively.

Several limitations should be noted when interpreting our findings. While we examined claims from 2004–2008 for evidence of metastatic bone disease, estimates of prevalence in this study cannot be properly interpreted as measures of the prevalence of 5-year history of metastatic bone disease, because not all individuals included in this study were continuously insured within the data sets studied. Of the commercially insured enrollees, 83.4%, 46.0%, 21.6%, 14.6%, and 11.1% had at least 1 year, 2 years, 3 years, 4 years, and 5 years of continuous coverage, respectively. The corresponding distribution of the fee-for-service Medicare enrollees was 93.3%, 86.1%, 79.7%, 74.2%, and 68.9%. Patients with relatively shorter duration of insurance coverage without claims evidence for metastatic bone disease may have had evidence of metastatic bone disease during the period without insurance coverage. The probable effect of examining less than 5 years of claims is underestimation of prevalence, as persons may be falsely identified as not having a history of metastatic bone disease. To explore this issue, we performed a post hoc analysis. We estimated separately in each cohort the crude probability of de novo evidence of metastatic bone disease in calendar year Y, given no evidence of metastatic bone disease from Y + 1 to 2008 and continuous enrollment from Y to 2008, for Y = 2004, 2005, 2006, and 2007. We used these probabilities to inflate prevalence estimates, such that the modified estimates could be interpreted as (extrapolated) measures of the prevalence of 5-year history of metastatic bone disease. We found that the number of persons with a 5-year history of metastatic bone disease could be as high as 322,180 (versus 279,679 in Table 3) US adults. These modified estimates

may be high, as the most common causes of non-continuous enrollment – a recent employment change in the non-elderly and a recent 65th birthday in the elderly – likely predict the absence of metastatic bone disease.

Second, not all diagnoses of metastatic bone disease result in corresponding claims codes. Few studies have examined the validity of using diagnosis codes to identify metastatic bone disease. The only such study we are aware of was done in Denmark and evaluated use of the ICD-10 code for metastatic bone disease (C79.5).[22] Using the National Registry of Patients database and data from medical chart reviews as the gold standard, Jensen et al[22] found relatively low sensitivity (0.44 [95% CI: 0.30–0.60] for prostate cancer and 0.32 [95% CI: 0.13–0.57] for breast cancer) and very high specificity. These results may not be applicable to the US experience. The ICD-10 diagnosis code set is substantially different in structure and concept from the ICD-9 code set, which is still in use in the United States. In addition, the coding practices may differ. Our use of codes for IV bisphosphonates relevant to treatment of metastatic bone disease to supplement the diagnosis code should help improve sensitivity, but this also presents limitations. For example, patients with kidney dysfunction or known risk factors for osteonecrosis of the jaw may not be candidates for bisphosphonate therapy. Additionally, patients who underwent orthopedic procedures or palliative radiation for a malignant fracture may not be identified by the codes used. Ultimately, the sensitivity and specificity of our claims-based definition of metastatic bone disease remains unknown until a validation study is performed.

Third, the age- and sex-specific prevalence estimates we applied to the US Census counts in each stratum were based on results from analysis of the commercially insured and fee-for-service Medicare populations. Prevalence of metastatic bone disease in the remainder of the adult population may differ from prevalence in the commercially insured and fee-for-service Medicare populations. Remaining subgroups of US adults include people with private insurance, uninsured people, Medicaid beneficiaries without Medicare coverage, Medicare Advantage participants, and military forces. The commercially insured and fee-for-service Medicare populations account for approximately 60% of the US adult population; the impact of possible differential prevalence in other subgroups is unclear.

A last important consideration in interpreting our estimates is that not all cases of metastatic bone disease are diagnosed. Patients with a poor prognosis at the time of cancer diagnosis might not receive tests for metastatic bone disease, with the rationale that they will die soon and

the information will not change treatment decisions. Other patients might develop asymptomatic metastatic bone disease and live with it for some time before it becomes symptomatic or is discovered during routine testing. This study reports only cases of metastatic bone disease that have come to the attention of health care providers and were recorded.

Despite these limitations, our data provide a recent perspective on prevalence of metastatic bone disease and increase knowledge about the distribution across cancer types.

Acknowledgments and disclosure

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