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ORIGINAL ARTICLE

Fractures frequently occur in older cancer patients: the MD Anderson Cancer Center experience

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Abstract
Purpose and Introduction A growing number of cancer patients are older adults aged 65 years and older. Patients with cancer are at increased risk for developing osteoporosis, falls, and fractures. We sought to identify the incidence of fractures in older adults who underwent cancer care between January 2013 and December 2015.
Methods A comprehensive geriatric assessment was performed, and bone densitometry was measured at baseline, with a 2-year follow-up.
Results In this study, among 304 patients with gastrointestinal, urologic, breast, lung, and gynecologic cancers we evaluated, and who completed the bone density testing ($n = 199$), 80% had osteoporosis or low bone mass (osteopenia). There was a higher prevalence of osteoporosis in cancer patients (40 vs. 16%, $p = 0.05$) than in population studies. Vitamin D insufficiency (< 30 ng/ml) was identified in 49% of tested cases ($n = 245$). Risk factors for low bone mass or osteoporosis were advanced age ($p = 0.05$), malnutrition ($p = 0.04$), and frailty ($p = 0.01$). Over the following 2 years (median follow-up 18 months), there was an incidence of fractures of 110 per 1000 person-years, or 2.8 times higher than reported in individuals without cancer. Risk factors for fractures included advanced age (70–79 vs. 60–69 years, $p = 0.05$) and frailty ($p = 0.03$).
Conclusion Most older cancer patients studied have osteoporosis or low bone mass, resulting in an almost 3-fold increase in fracture risk as compared to epidemiologic studies. Bone health issues are commonly seen in older cancer patients, we recommend universal bone density testing. The initiation of antiresorptive treatment when findings are of osteopenia or osteoporosis will reduce the risk of fractures.

Keywords Malignancy · Fractures · Falls · Low bone mass · Older adults

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Introduction

More than 60% of cancer patients are older adults 65 years of age and older—by 2020, this could rise to 70%. Age-related diseases such as bone loss and osteoporosis [1] will complicate cancer management. Superimposed on age-related bone loss, cancer treatment-induced bone loss (CTIBL) accelerates bone loss [2]. CTIBL results in a higher risk for fracture; in the Women's Health Initiative, women with BC had a 55% increased risk for hip fractures [3], and a 2-fold increase in fracture risk in other solid tumors (lung cancer, lymphoma, skin cancer, and endometrial cancer) [3]. Prior studies illustrate that fractures are a major cause of morbidity, functional decline, nursing home admissions, and mortality, in a cancer-

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free population. The cost of osteoporosis to the American healthcare system is estimated to be approximately 19 billion dollars annually, with a large proportion of the cost being attributed to hip fractures [4]. There is currently a paucity of data on fracture cost in the cancer population.

In addition, older adults exhibit "geriatric" conditions that increase fractures. Falls are common in older adults, and approximately 30% of women sustain a fall in a given year [5]. Fried et al. [6] defined frailty as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss, self-reported exhaustion, weakness (low grip strength), slow walking speed, and low physical activity [7]. Frailty represents a decline in multiple systems, caused by a mixture of physiological, psychological, social, and environmental factors, such as sarcopenia, functional impairment, cognitive impairment, and depression, and contributes to adverse health outcomes. Frailty, in individuals without cancer, has been suggested to be a risk factor for fractures.

Recommendations for management of CTIBL have focused on patients on adjuvant hormonal therapies; in the NCCN Clinical Practice Guidelines (NCCN Guidelines) for Breast and Prostate Cancers, evaluation with baseline and periodic bone density (BMD) testing is recommended [8]. The NCCN Guidelines recommend screening according to the National Osteoporosis Foundation (NOF) guidelines for the general population [8]. NOF recommends bone density testing in all women and men at 65 and 70 years in those without risk factors [9]. Earlier screening would be appropriate in those with conditions such as rheumatoid arthritis or using medications such as corticosteroids associated with bone loss [9]. ASCO guidelines add that BMD screening should be incorporated for women with breast cancer who have high-risk factors [10]. Pharmacologic treatment is recommended if the T score is ≤ -2.0 at the lumbar spine, femoral neck, or total hip site or if the WHO Fracture Risk Assessment (FRAX) 10-year absolute risk of fracture is greater than 20% for any major fracture or greater than 3% for hip fracture, respectively [8]. A joint statement from multiple organizations reiterates the need to screen women with breast cancer initiating aromatase inhibitors [11], while the EMAS guidelines recommend a bone density test at the time of breast cancer diagnosis [12].

Antiresorptive medications have positive effects on bone health in cancer patients. Denosumab prevents vertebral fractures in individuals with breast cancer (50% fracture reduction) and prostate cancer (61% fracture reduction) on adjuvant hormonal therapy [13–15]. Bisphosphonates prevent CTIBL and increase BMD, but given smaller studies, have had limited power to demonstrate fracture prevention [16–19]. In non-cancer populations, all osteoporosis medications reduce fracture risk and improve survival after a fracture [20–22]. Antiresorptive therapies have a more rapid onset of action than other common medical therapies [23].

This study evaluated the incidence of osteoporosis, low bone mass, and fractures among older cancer patients seen in the Program for Healthy Aging at MD Anderson from January 1, 2013, to December 31, 2015. We postulate that low bone mass and osteoporosis in this older adult cohort will lead to a higher incidence of fractures, placing cancer patients and survivors at higher risk of adverse clinical consequences.

Methods

The research protocol was approved by the institutional review board. Data was prospectively collected in all older adults referred to the Program for Healthy Aging—aged 65 years of age and older. Patients were community dwelling and ambulatory, presented solid tumors, or were hematologic malignancy candidates for stem cell transplantation. Individuals were evaluated from January 1, 2013, through December 31, 2015, at the Program for Healthy Aging for geriatric assessment. Individuals were referred prior to undergoing allogeneic stem cell transplantation, radical cystectomy, or gastrointestinal surgery, or at different points of care for breast, prostate, lung, and skin cancer. Patients were not referred for osteoporosis or palliative or end-of-life care.

Bone densitometry (Discovery W, Hologic Corp., Marlborough, MA) of the lumbar spine (L1–L4), total hip, and femoral neck was measured. Patients were considered to have osteoporosis if their adjusted T scores are equal to or less than -2.5 at any measurement site. The coefficient of variation, important for serial testing, of spine was 1% and hip 1.5%. Bone mineral density (BMD) testing (dual-energy x-ray absorptiometry (DXA)) was ordered in all older adults seen in the Program for Healthy Aging, unless they had a DXA in the preceding 12 months.

The geriatric assessment was conducted to identify other geriatric syndromes such as frailty, cognitive impairment, and malnutrition that may be contributing to the higher risk of fractures. Assessment included functional assessment: Katz' activities of daily living (ADL) [24] and Lawton's independent activities of daily living (IADL) [25], depression screening utilizing the Patient Health Questionnaire 9 (PHQ-9), and balance and gait using the Short Physical Performance Battery; frailty was assessed utilizing Fried's criteria [6, 26], and cognition was assessed with the Montreal Cognitive Assessment. Falls within the prior 6 months were self-reported. Geriatric assessment scales have been previously validated.

Recommendations for a calcium- and protein-rich diet as well as calcium and vitamin D3 supplementation were made. Individuals with vitamin D deficiency were treated according to clinical guidelines. Patients were to return to the office for treatment 2 weeks after DXA was conducted, or individuals were scheduled for allogeneic stem cell transplantation,

1 month after transplantation. Additionally, individuals with low bone mass or osteoporosis were reminded via telephone and the patient portal *mymdanderson* of the need for further treatment for these conditions. The incidence of osteoporosis in patients with cancer was compared to the National Health and Nutrition Examination Survey (NHANES III) for the decade of 70–79 years of age [27].

Duration of follow-up Patients were followed from 6 months to 2 years.

Fracture ascertainment Electronic medical records were searched for radiographic reports denoting fractures; images were further validated by skeletal radiologists. Only fractures seen at MD Anderson were included in this study. Self-reported fractures without radiographic confirmation were excluded. Pathologic or metastatic fractures were excluded from this analysis. Research staff determined metastatic fractures by terminology used (pathologic, metastatic) and subsequent terminology in notes or procedures such as radiation therapy, or initiation of chemotherapy over the following 12 months.

Analysis Patient demographics, bone density test results, and other clinical characteristics were summarized according to presence or absence of a new fracture using descriptive statistics. Time to new fracture, a time interval from the CGA test to new fracture, was calculated for patients with a new fracture. Patients without a new fracture were censored at the time of last follow-up or date of death. Univariate and multivariable Cox proportional hazards regression analyses were performed to identify factors associated with increased risk of new fracture. A p value of less than 0.05 indicated statistical significance. SAS 9.4 (SAS Institute INC, Cary, NC) was used for data analysis.

Results

We analyzed patients with solid tumors and hematologic malignancies ($n = 304$). The most common cancers were gastrointestinal, urologic, and breast cancer, followed by lung cancer and gynecologic cancers; remaining cases were divided among skin, endocrine, and neurologic cancers. The median follow-up time is 8.8 months (95% CI, 8.0–10.8 months). Baseline characteristics are summarized in Table 1. Among 304 patients, 31 (10%) had a new fracture and 273 did not have a new fracture. Sites of fractures comprised ribs (14), vertebrae (8) (morphometric vertebral fractures were not included), humerus (3) and hip (5). The mean age for those who had a fracture was 79.3 ± 5.8 years, and 78.3 ± 7.0 years in those without a new fracture. Incidence of new fracture was 110 events per 1000 person-years (31 events/3265.35 person-months) (95% CI, 77–162 events per 1000 person-years). The incidence rate ratio of our study population is 2.8-fold higher (CI 95, 1.93–4.03, $p = 0.000$) compared to the incidence rate ratio of individuals from a national epidemiologic study [NHANES], aged 70–79 years [28]. The probability of sustaining a fracture increased with time (Fig. 1).

Bone mineral density was ordered in all but completed in only 191 (63%) patients. The incidence of low bone mass and osteoporosis in the tested group was 80% (155 out of 191) and similar in both genders (31% had osteoporosis, and 45%, low bone mass). Of the patients with fractures, 13 had osteoporosis, 6 low bone mass, and 10 had normal BMD. Thirty-five percent of patients reported prior fractures. There was a higher incidence of osteoporosis in cancer patients as compared to the age-specific incidence of osteoporosis in an epidemiologic study (70–79 years of age) (37 vs. 16%, $p = 0.05$). Multivariate analysis elucidated risk factors for low bone mass or osteoporosis (analysis not shown) including advanced age ($p = 0.05$), malnutrition ($p = 0.04$), and frailty ($p = 0.01$). Falls were frequently reported, with over 50% cases having one or more falls in the preceding 6 months, as compared to community-dwelling older adults with 30% falls in the past 12 months. Vitamin D insufficiency (< 30 ng/ml) was encountered in 125 out of 256 subjects (49%) (Table 1).

Univariate and multivariable Cox regression models for fractures are presented in Table 2. Older-age groups (75–84 years compared to 65–74 years), low bone mass compared to osteoporosis, and frailty compared to frailty-free showed significant associations with an increased risk of new fracture according to univariate Cox regression analyses. Falls in the preceding 6 months showed a trend toward significance with increased risk of fracture ($p = 0.07$). The multivariable model included age group, old fracture, and frailty with a univariate p value < 0.15 and with no missing values. Frailty remained significant with the risk of new fracture. Age group and prior fracture were not significant. The backward elimination method was applied to reduce the multivariable model, and the only variable remaining in the model was frailty.

Discussion

In cancer care, we strive to provide cancer patients with the highest possible quality of life. The challenge in older adults is that bone health may be playing a sizable, yet, underestimated role. Fractures result in morbidity, functional impairment, and mortality. Hip and other fractures result in a profound threat to quality of life, and in trade-off studies, women would prefer the choice to be dead than to be institutionalized in a nursing home after a hip fracture [29]. Our study reveals that older adults with cancer present an unusually elevated fracture rate, 2.8 times higher than that seen in epidemiologic studies in a comparably aged population.

Table 1 Baseline characteristics by fracture group

Variable	Characteristics	New fracture ($N = 31$)	Fracture-free ($N = 273$)
Gender	Female	20 (65%)	139 (51%)
	Male	11 (35%)	134 (49%)
Age	Mean ± SD	79.3 ± 5.84	78.3 ± 7.03
	65–74	5 (16%)	89 (33%)
	75–84	20 (65%)	130 (48%)
	85 and older	6 (19%)	54 (20%)
Race[a]	Black/African American	4 (13%)	49 (18%)
	Other	1 (3%)	12 (4%)
	White	26 (84%)	205 (77%)
Ethnicity[b]	Hispanic or Latino	3 (12%)	26 (11%)
	NOT Hispanic or Latino	22 (88%)	205 (89%)
Smoking[c]	Current smoker	2 (7%)	11 (4%)
	Former smoker	10 (33%)	109 (43%)
	Non-smoker	18 (60%)	131 (52%)
Alcohol[d]	Heavy drinker	0 (0%)	5 (2%)
	Non-drinker	23 (82%)	167 (67%)
	Occasional drinker	3 (11%)	52 (21%)
	Regular drinker	2 (7%)	24 (10%)
Cognitive impairment[e]	Dementia	13 (42%)	84 (31%)
	MCI	11 (36%)	87 (33%)
	Normal	7 (23%)	97 (36%)
Cognitive impairment[e]	Dementia/MCI	24 (77%)	171 (64%)
	Normal	7 (23%)	97 (36%)
Bone density diagnosis[f]	Osteoporosis	13 (62%)	57 (34%)
	Low bone density	5 (24%)	80 (47%)
	Normal	3 (14%)	33 (19%)
Bone density[f]	Osteoporosis/low bone	18 (86%)	137 (81%)
	Normal	3 (14.3%)	33 (19.4%)
Vitamin D[g]	Insufficiency (< 30)	16 (57%)	109 (48%)
	Normal	12 (43%)	119 (52%)
25 (OH) vitamin D (ng/ml)[g]	Mean ± SD	31.6 ± 17	34.8 ± 44
BMI[h]	Mean ± SD	27 ± 7	27 ± 6
Prior fracture	Yes	8 (26%)	36 (13%)
Fall in the last 6 months[i]	Never	11 (46%)	127 (67%)
	Ever	13 (54%)	64 (34%)
CCI[j]	0–5	21 (68%)	182 (67%)
	> 5	10 (32%)	89 (33%)
Frailty	Yes	17 (55%)	90 (33%)
Malnutrition	Yes	15 (48%)	122 (45%)

BMI body mass index, *CCI* Charlson comorbidity index, *25(OH) vitamin D* 25 hydroxy vitamin D

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Approximately 80% of older cancer patients had low bone mass or osteoporosis. Advanced age and frailty were identified as risk factors for fractures. Fractures were seen equally in both genders. Given the growing number of cancer patients who are 65 years of age and older, we would consider that a recommendation for bone density screening in older adults with cancer should be further highlighted in oncology and the supportive oncology field. Our findings identify that fractures are exceedingly common in older cancer patients. Early diagnosis would allow for initiation of osteoporosis medications. Medications for osteoporosis can prevent cancer treatment-induced bone loss, and denosumab prevents vertebral fractures.

The etiology of bone loss in older cancer patients is likely multifactorial, with age-related bone loss and cancer therapy-induced bone loss playing a role [2]. Inflammation is a

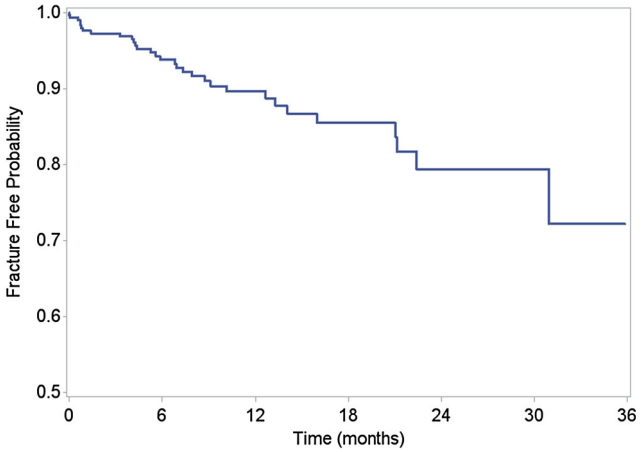

Fig. 1 The probability of sustaining a fracture by time

hallmark of cancer, and results in accelerated bone loss [30]. The role of cyclooxygenase, prostaglandin E2, and other mediators in cancer-associated inflammation has been well established [3], hastening bone decline. Cancer therapy exerts a deleterious effect on bone health via gonadal suppression from chemotherapy or hormonal therapy [2]. Chemotherapy directly accelerates bone loss [2] and results in a higher fracture risk. Corticosteroids are associated with upregulation of osteoclast function and downregulation of osteoblast function, leading to changes in bone quality and increased fracture risk [2].Radiation therapy can have a direct local effect on bone; for example, chest irradiation and pelvic irradiation are associated with an increased risk of rib fractures and pelvic insufficiency fractures [8]. Lifestyle factors commonly encountered in cancer patients such as fatigue, sedentary lifestyle, low dietary calcium intake, weight loss, frailty, and malnutrition will additionally contribute to rapid bone loss.

Decreased mechanical loading plays a role in cancer-related bone loss, often caused by cancer-related fatigue and sedentary lifestyle [31–33]. Often termed *disuse osteoporosis*, this term refers to bone mass decrements under conditions of decreased mechanical loading, including decreased ground force reaction, muscular contraction, and microgravity-related bone loss in astronauts after space flights or prolonged inactivity as in cases of spinal cord injury. The response to mechanical loading is mediated via *wnt* pathway signaling [31–33]. Osteocytes lie within the bone in an interconnected network that positions them to sense and respond to local biomechanical and systemic stimuli to regulate bone remodeling and adaptation [34]. The remodeling process provides a mechanism for adapting the skeleton to local biomechanical factors and systemic hormonal influences and for replacing bone that has undergone damage from repetitive mechanical loading [34]. More recently, muscle loss or sarcopenia, commonly seen in cancer patients, has been identified in older adults as a contributing element in fracture risk [35].

Older cancer patients exhibit a number of conditions that increase the risk of falls and consequently fractures, such as frailty, vitamin D insufficiency and deficiency, and cognitive impairment (mild cognitive impairment and dementia). The syndrome of frailty, that is, the occurrence of combined malnutrition and sarcopenia, has been shown to predict adverse clinical outcomes and must be addressed in order to prevent falls and fractures with a multimodality approach. This combines nutrition and rehabilitation. Thus, developing interventions for older adults will contribute to improved outcomes. Although clinicians may have some concern about life expectancy and onset of action of osteoporosis medications, medications for osteoporosis are highly effective, have a more rapid onset of action than other common medical interventions, and reduce vertebral fracture risk as early as 6 months after initiation of therapy. Vitamin D deficiency is associated with a higher risk for falls and likely fractures, and vitamin D replacement is associated with improvement in lower extremity strength, and reduces the risk of falls. Dementia such as Alzheimer's disease has been associated with a higher fall and fracture risk [36, 37]. The use of proton pump inhibitors, anticoagulants, and antidepressants, often used by individuals with cancer, is conducive to fractures [8]. Therefore, the management should not only include treatment for low bone mass but also address these additional conditions.

Areas for improvement include interventions to prevent falls. It is known that less than 10% of cancer patients who report falls are referred for appropriate management [38]. Individuals who report falls should undergo gait and balance assessment, have a vitamin D level tested, and referred for physical therapy for gait and balance training, as well as strengthening exercises. Vitamin D deficiency should be corrected. A combination of nutrition intervention and exercise and physical therapy may address frailty in order to prevent falls. Home safety evaluation by physical or occupational therapists and interventions is beneficial such as removing throw rugs and cords, and providing lighting and railings.

Fractures occur in patients with low bone mass and in those with osteoporosis, being less common in older adults with normal bone density [3]. It is important to consider that in the ABCSG-18 study, even women with normal bone density on aromatase inhibitors sustain fractures, and denosumab use significantly reduces the risk of fractures [15]. Our results highlight that in the majority of older patients with cancer, there is some degree of bone loss. Fractures most often occur in those with osteoporosis or low bone mass (osteopenia) [39, 40]. Thus, we advocate that cancer bone health guidelines recommend bone density testing in older adults with cancer. The initiation of antiresorptive therapy in individuals with low bone mass or osteoporosis would reduce the risk of fractures and lead to improved clinical outcomes.

The majority of patients identified to be at risk for fractures were recommended to return to the clinic, yet

Table 2 Risks of new fracture according to univariate and multivariable regressions

		Univariate Cox regression				Multivariable model ($N = 304$)			
Variable		HR	95% CI		*p* value	HR	95% CI		*p* value
Gender	Female	1.6	0.78	3.38	0.31				
	Male	Ref							
Age	In 1-unit change	1.0	0.98	1.09	0.20				
	65–74	Ref				Ref			
	75–84	3.0	1.12	7.96	0.03	2.63	0.98	7.01	0.05
	85 and older	2.6	0.76	8.31	0.12	2.02	0.60	6.79	0.26
Race[a]	Black/African American	0.6	0.19	1.62	0.32				
	Other	0.7	0.09	5.43	0.81				
	White	Ref							
Ethnicity[b]	Hispanic or Latino	1.11	0.32	3.55	0.94				
	NOT Hispanic or Latino	Ref							
Smoking[c]	Current smoker	1.7	0.40	7.58	0.52				
	Former smoker	0.8	0.38	1.81	0.61				
	Non-smoker	Ref							
Alcohol[d]	Heavy drinker	0.000	0.0	.	0.92				
	Non-drinker	1.2	0.29	5.30	0.81				
	Occasional drinker	0.6	0.09	3.33	0.53				
	Regular drinker	Ref							
Cognitive impairment[e]	Dementia	2.0	0.77	5.03	0.14				
	MCI	1.6	0.61	4.05	0.35				
	No	Ref							
Cognitive impairment[e]	Dementia/MCI	1.5	0.81	4.13	0.18				
	No	Ref							
Bone density diagnosis[f]	Osteoporosis	2.5	0.72	8.87	0.15				
	Low bone mass density	0.8	0.19	3.33	0.76				
	Normal	Ref							
Bone density diagnosis[f]	Osteoporosis/low bone mass	1.6	0.46	5.34	0.47				
	Normal	Ref							
Vitamin D[g]	Insufficiency (< 30)	1.2	0.58	2.59	0.61				
	Normal	Ref							
25 (OH) vitamin D (ng/ml)[g]	In 1-unit change	1.0	0.98	1.02	0.95				
BMI[h]	In 1-unit change	1.0	0.92	1.05	0.58				
Prior fracture	No	Ref				Ref			
	Yes	1.8	0.82	4.11	0.14	1.62	0.71	3.64	0.25
Fall in the last 6 months[i]	Never	Ref							
	Ever	2.1	0.93	4.65	0.07				
Comorbidity[j]	0–5	Ref							
	> 5	1.0	0.47	2.13	0.99				
Frailty	Yes	2.4	1.20	4.91	0.01	2.31	1.10	4.66	0.03
Malnutrition	Yes	1.3	0.65	2.65	0.45				

[a] Frequency missing = 7

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failed to return for initiation of osteoporosis therapy (150/199). Thus, diagnosed, yet untreated, they remained at high risk for fractures and functional decline. A greater awareness in the cancer community of the disabling effect of fractures should motivate cancer specialists to counsel patients about the need for bone health assessment and treatment. Antiresorptives, bisphosphonates, and receptor activators of the nuclear factor kappa-B ligand have demonstrated a reduction in cancer therapy-related bone loss; for denosumab, the prevention of vertebral fractures. Concerns in the cancer community about renal toxicity may be addressed by the use of denosumab, which is

approved in the presence of chronic kidney disease. Bisphosphonate guidelines in cancer care have resulted in a reduction in the risk of acute kidney injury [41]. Guidelines on osteonecrosis of the jaw, and the rare occurrence of atypical femur fractures in cancer care, should promote judicious use of osteoporosis medications. The long-term safety of bisphosphonates has been evaluated by the American Society of Bone and Mineral Research [42].

Limitations of our study include being a single-site retrospective study, potential sample enrichment due to referral pattern, and lack of a control population given that the site is a cancer center where the patients seen all had cancer diagnosis. Fracture cases could be underestimated as patients may seek treatment elsewhere. There may have been inaccuracies in comparison with the NHANES III population due to methodological differences. The patient selection bias may exist due to referral pattern, and our study population may not be well represented to compare with national data in terms of relative risk ratio. Larger studies may allow for the identification of additional risk factors for fractures in older cancer patients. We would suggest that going forward prospective studies be conducted.

Conclusions

A large proportion of older cancer patients who have undiagnosed osteoporosis or low bone mass exhibit an incidence of fracture that is 2.8 times higher than that seen in older adults in epidemiologic studies such as the National Health and Nutrition Survey (NHANES) III. Cancer therapy-induced bone loss and the presence of geriatric syndromes such as frailty contribute to the elevated fracture rate. We propose bone density testing and initiation of antiresorptive therapy in older cancer patients with osteoporosis or low bone mass in order to prevent fractures and maintain a higher quality of life.

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Compliance with ethical standards

The research protocol was approved by the institutional review board.

Conflict of interest The authors declare that they have no conflict of interest.

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