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Bone Health and Survival in Women With Multiple Myeloma

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Abstract

Osteoporosis is highly prevalent, and how this comorbidity contributes to outcomes in individuals who develop multiple myeloma (MM) is unknown. Using the Women's Health Initiative dataset (n = 362), factors were evaluated in women who later developed MM. Higher fracture risk, measured by the Fracture Risk Assessment Tool, was associated with higher mortality (covariate-adjusted hazard ratio, 1.51; 95% confidence interval, 1.01–2.25; P = .044) in postmenopausal women who develop MM, independent of other clinical factors.

Background: Multiple myeloma (MM) is a disease of aging adults resulting in osteolytic and/or osteoporotic bone disease. Primary osteoporosis is also highly prevalent in aging adults and is associated with increased mortality. It is unknown how concurrent osteoporosis is associated with outcomes in patients who develop MM.

Patients and Methods: We identified 362 women with MM of the 161,808 enrolled in the Women's Health Initiative (WHI) dataset and evaluated bone health using the Fracture Risk Assessment Tool (FRAX) to identify clinical factors that affect overall MM survival in postmenopausal women, as measured from the time of diagnosis.

Results: Of the 362 participants who developed incident MM, with an average 10.5 years of follow-up, 226 died, including 71 with high FRAX scores and 155 with low FRAX scores. On average, women with high FRAX scores were 8.3 years older at enrollment (95% confidence interval [CI], 7.2–9.3 years) and 8.0 years older at time of MM diagnosis (95% CI, 7.0–9.2 years) compared with those with low FRAX scores. MM mortality for women with high FRAX scores

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The authors have stated that they have no conflicts of interest.

Supplemental Data

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was greater (covariate-adjusted hazard ratio scores [aHR] 1.51; 95% CI, 1.01–2.25; $P = .044$) compared with those with low FRAX scores.

Conclusion: Higher fracture risk, measured by FRAX, was associated with higher MM mortality in post-menopausal women, independent of many other clinical factors.

Keywords

FRAX; Geriatric; MGUS; Multiple myeloma; Osteoporosis

Introduction

Multiple myeloma (MM) is an incurable hematologic malignancy that causes osteolytic and osteoporotic bone disease. MM is a disease of older adults, where the incidence of osteoporosis is also very common. Osteoporosis is a significant comorbidity, associated with an excess of mortality in the general population secondary to fractures.^{1,2} It is unknown how pre-existing bone disease contributes to clinical outcomes in individuals who develop MM. The standard diagnostic evaluation for MM does not include dual-energy x-ray absorptiometry (DXA); therefore, assessments of underlying osteoporosis are not routine.³ Primary osteoporosis is the deterioration of bone unassociated with other chronic illness and is multifactorial, related to aging and decreased gonadal function, among other factors.⁴ Secondary osteoporosis results from conditions that accelerate bone loss; as in the example of unopposed osteolysis induced by malignant plasma cells.^{5–7}

Clinically, distinguishing osteoporotic fragility fractures from pathologic MM-induced fractures is challenging. Myeloma bone lesions can be detected by skeletal x-rays (surveys) and denote the need for treatment. Skeletal surveys underestimate bone involvement by approximately 40% and are even less specific for distinguishing myeloma-related secondary osteoporosis from primary osteoporosis.⁸ Consequently, other imaging modalities, including magnetic resonance imaging (MRI), are useful to differentiate benign versus malignant vertebral fractures using morphologic criteria,⁹ although two-thirds of malignant vertebral fractures by MRI appeared benign at diagnosis.¹⁰ Identifying osteolytic disease in MM can be further refined using computed tomography or positron emission tomography-computed tomography guided imaging.³ However, osteoporosis is a silent condition, where, if not clear by patient history, may obfuscate the need for further imaging in an oncology practice.

As such, we sought to examine the relationship of fracture probability defined by the Fracture Risk Assessment Tool (FRAX)¹¹ and mortality in individuals who develop MM. The FRAX instrument can be used to detect fracture probability and indicate the need for treatment for osteoporosis, independent of BMD testing.^{12,13} Utilizing data from the Women's Health Initiative (WHI), we examined the relationship between FRAX and the risk of death in women who developed MM. Analysis included detailed data regarding participants' medical history, osteoporosis-related cofounders, myeloma development, and social and lifestyle influences. The purpose of this study was to evaluate the impact of pre-existing bone health and prognostic factors that affect overall MM survival.

Patients and Methods

Study Population

The WHI is a longitudinal study of 161,808 postmenopausal women originally recruited at 40 clinical centers across the United States from 1993 to 1998. Women were either enrolled in the WHI Observational Study (OS) or randomized into 1 or more clinical trials (CT) that could include estrogen plus progestin or estrogen-alone therapy, dietary modification, and/or calcium and vitamin D supplementation. Women were between the ages of 50 and 79 years at recruitment and had to be postmenopausal at baseline. In 2005, after the completion of all WHI clinical trials, women in both the OS and the CT components were re-consented for the first WHI extension (2005–2010) and then again from 2010 to 2015 for the second WHI extension. Complete WHI study details are provided elsewhere.¹⁴ We investigated survival following development of MM in the WHI OS and CT studies through the first extension period of follow-up (2010). WHI women with a prior history of cancer were excluded. MM cases were reported and physician-adjudicated according to WHI procedures where MM cancer is coded for tumor behavior (if known), diagnostic confirmation, and reporting source. Date of diagnosis was by diagnostic confirmation status; full adjudication methods have been previously published.¹⁵

Bone Health

The FRAX tool (US FRAX version 3.0) is a web-based algorithm that calculates 10-year probability of hip fracture and other major osteoporotic fractures in men and women based on clinical risk factors and, optionally, bone mineral density (BMD) of the femoral neck.¹⁶ FRAX is an established instrument to assess fracture probability in diverse patient populations, and the model refines fracture risk prediction beyond BMD alone.^{17–19} FRAX scores were calculated without inclusion of BMD values, and missing variables were defaulted as recommended by the World Health Organization Center (“no” for categorical variables, mean value of the cohort for continuous variables).²⁰ BMD by DXA was measured at only 3 of the 40 clinical centers and therefore was not included in the FRAX calculation for this study. Clinical osteoporosis risk factors included in the FRAX score were: age, gender, weight, height, race, rheumatoid arthritis, history of prior fracture, glucocorticoid use, smoking, alcohol intake, parental history of hip fracture, and secondary osteoporosis (defined as type 1 diabetes, osteogenesis imperfecta, hyperthyroidism, hypogonadism, premature menopause, chronic malnutrition, malabsorption, chronic liver disease). These risk factors were taken from baseline WHI self-assessment questionnaires and weight and height measurements at the time of enrollment. According to the 2008 National Osteoporosis Foundation recommendations, treatment of osteoporosis should be considered for patients who meet any of the following parameters; personal history of hip or vertebral fracture; T-score of -2.5 or lower at the femoral neck or spine; T-score of between -1.0 and -2.5 at the femoral neck or spine, and a 10-year hip fracture risk of $\geq 3\%$ or a 10-year risk of a major osteoporosis-related fracture of $\geq 20\%$ as assessed with the FRAX.¹⁶ A high FRAX score for our study population was defined as a score with 10-year probability of hip fracture $\geq 3\%$ or a major osteoporosis related fracture $\geq 20\%$. For our population, FRAX high women are considered a high-risk population that would meet a threshold for requiring a treatment intervention for osteoporosis. FRAX scores were estimated at the time

of WHI enrollment (baseline). For comparison, simplified calculators of osteoporosis risk were also analyzed using Osteoporosis Self-assessment Test (OST).²¹ The OST uses weight and age and was calculated using the formula $0.2 \times (\text{weight in kg} - \text{age in years})$. An OST score below 2 was defined as high osteoporosis risk for women, with a reported sensitivity of 88% (95% confidence interval [CI], 83%–93%) and a specificity of 52% (95% CI, 49%–55%).²²

Overall Survival

Overall survival was defined from the day of MM diagnosis to the date of death, or last follow-up, through 2010, the first WHI extension period.

Statistical Methods

Baseline and follow-up data, including information on death and fracture, were examined. Descriptive analyses compared baseline characteristics by the primary risk factor, high FRAX score. For the purpose of this analysis, low FRAX scores refer to those with both low and intermediate probability of fracture. Comparisons between categorical characteristics were made by Fisher exact tests and, for continuous characteristics, through a 2-sample *t* test, assuming unequal variances. We examined the influence of osteoporosis measures on the risk of overall survival. Primary model development focused on estimating the relationship between FRAX score and survival following MM diagnosis, with adjustment for characteristics expected to be potential confounders associated with FRAX score and risk of death after MM diagnosis. Cox proportional hazards models^{23,24} were used to estimate the risk of death associated with each risk factor (FRAX risk score high/low or OST high risk) while adjusting for demographics and a priori specified confounding factors, including race, education, baseline body mass index (BMI), diagnosis of rheumatoid arthritis, menopausal hormone use, calcium supplementation, and vitamin D supplementation at baseline. Cox models included stratification of the baseline hazard by age group at diagnosis and study membership (OS/CT). The assumption of proportional hazards was examined graphically by examining the cumulative baseline incidence rate and tested through tests of Schoenfeld residuals after model estimation. All presented *P*-values and confidence intervals are 2-sided and unadjusted for multiple comparisons. Analyses were conducted in STATA (version 13, StataCorp, College Station, TX) and SAS version 9.4, SAS/STAT 13.2 (SAS Institute, Inc, Cary, NC). All analyses use WHI follow-up datasets distributed in November, 2016.

Results

Demographics by FRAX

A total of 161,808 women enrolled in WHI; of these, 409 women developed MM, of which 362 did not have a history of any cancer at baseline and were included in this analysis. At baseline, women with MM were classified as having high FRAX (*n* = 98; 27%) or low FRAX scores (*n* = 264; 73%). Women with high FRAX scores were older on average at enrollment and at the time of MM diagnosis (average of 8.3 years older at enrollment; 95% CI, 7.22–9.31 years; *P* < .001 and an average of 8.0 years older at MM diagnosis; 95% CI, 6.95–9.19 years; *P* < .001). Women with high FRAX scores were more often white (*n* = 93; 95%) and had lower BMI on average (average difference of 3.7; 95% CI, 2.6–4.8; *P* < .001).

However, there was no substantial difference observed in self-reported physical activity, as measured by METS (average difference 2.3 units; 95% CI, 0.7–5.4 units; $P = .109$). No significant differences were identified among baseline characteristics such as ever use of hormones, education, smoking, region, self-report of osteoporosis, parental bone fracture, calcium/vitamin D supplementation, or clinical trial participation in high versus low FRAX women (Table 1).

Of the 362 patients who developed MM, 226 died during the follow-up period, including 71 with high FRAX scores (31% of the total number of deaths and 72% of those with high FRAX) and 155 with low FRAX scores (69% of the total number of deaths and 59% of those with low FRAX). The median follow-up time was 10.5 years (range, 0.4–16.4 years) from enrollment, and 7.2 years (range, 0.04–15.7 years) from the time of MM diagnosis (Figure 1). The adjusted risk of death was increased among women with high FRAX scores (aHR, 1.61; 95% CI, 1.09–2.38; $P = .018$) compared with those with lower scores (Figure 2). In multivariable analysis, the risk of death was adjusted for age group at MM diagnosis and WHI study membership (OS/CT) (see Supplemental Table 1 in the online version). High-risk OST scores (< 2) were not associated with an increased risk of death compared with low-risk scores (aHR, 1.23; 95% CI, 0.77–1.95; $P = .388$). A sensitivity analysis excluded 18 patients who were diagnosed with MM in the first year after study enrollment. Results did not substantially change with this exclusion. A further sensitivity analysis was conducted to explore factors related to time to diagnosis from the date of recruitment into WHI. These factors may help to understand if underlying osteoporosis delays time to MM diagnosis. In our analysis, none of the measures of bone health, including FRAX, were predictive of the time to MM diagnosis.

WHI participants reported fractures during follow-up. In our study sample, 57 fractures occurred during evaluation. The majority of fractures were reported prior to MM diagnosis ($n = 35$; 65%). Less than one-half of women developed a first observed fracture after diagnosis ($n = 22$; 39%). The probability of fracture was similar among women with high and low FRAX scores (17 [17.4%] fractures in those with high FRAX vs. 40 [15.2%] fractures in those with low FRAX [HR, 0.99; 95% CI, 0.45–2.18]), although these events account for all fractures before and after diagnosis.

Discussion

Osteoporosis is highly prevalent in aging adults, and very little is known on how this comorbid condition contributes to outcomes in individuals who develop myeloma. MM skeletal-related events (SREs) are painful, and debilitating complications include pathologic fractures, spinal cord compression, and the need for radiation or surgical repair. More than one-half of MM patients will develop an SRE during their lifetime, and SREs are a major cause of morbidity and mortality.^{25,26} The prevalence of primary osteoporosis can confound the diagnosis of MM. Here we report that poor bone health (by FRAX) is associated with greater MM mortality. This increase in MM mortality is not related to delay in time to diagnosis. Fracture reports were similar in women with high/low FRAX scores; however, this includes fractures both before and after MM development. Furthermore, the receipt of

bisphosphonates is not known in this analysis of women who participated in WHI. Our data report the MM survival differences in women with pre-existing high-risk bone disease.

Our study has several potential limitations. The WHI does not include information on diagnostic or treatment differences in the MM population studied specifically regarding staging, chemo-therapy treatment, and/or use of bisphosphonates. Use of bisphosphonates may mitigate fracture development. Furthermore, it is not known if individuals were known to have pre-existing monoclonal gammopathy of undetermined significance (MGUS). MGUS is an asymptomatic clonal plasma cell disorder that occurs in approximately 3% of the aging population and progresses to MM in 1% of the population per year.²⁷ Several studies have outlined that nearly all patients diagnosed with MM have preceding MGUS, where a monoclonal protein can be detected up to 8 years prior to diagnosis of MM.²⁸ MGUS is associated with a higher incidence of osteoporosis²⁹ and an increased fracture risk,³⁰ where vertebral fractures were 6.3-fold more prevalent in patients with MGUS compared with the general population³¹ and increased in post-menopausal women with MGUS.³² We can speculate that many of the women in our study population had pre-existing MGUS. MGUS is established to have compromised cortical bone architecture^{33,34} and reduced bone strength and thus is plausible to result in poor bone health (high FRAX scores) and result in inferior survival in our population. However, a thorough examination of fracture risk after MM diagnosis was not possible because only the first observation of fracture is recorded in WHI follow-up, which occurred in many individuals prior to MM diagnosis.

Optimizing skeletal care in patients with MM, once diagnosed, is well-studied and is an essential aspect of management. Bisphosphonates are recommended for all patients with MM with and without identified lytic bone disease or those with osteoporosis (grade A) or osteopenia (grade C).³⁵ However, 25% to 31% of patients with MM do not have bone disease at the time of diagnosis.³⁶ It is unknown if bisphosphonates offer any advantage without clear bone disease by MRI or positron emission tomography.³⁵ Routine use of skeletal x-rays are performed at diagnosis; however, preferred measures of osteoporosis evaluation such as DXA are not routinely done at myeloma diagnosis.³ Here, we report that older post-menopausal women with a lower BMI are those who are most likely to have high FRAX scores and adverse outcomes. The number of women who developed any fracture during WHI follow up was 57, and more than one-half of these fractures occurred prior to MM diagnosis. This is consistent with others' work reporting increased fracture risk with MGUS and MGUS prevalence with osteoporosis.^{33,34} The FRAX tool is useful to estimate an individual fracture probability in 10 years with or, as in this study, without use of the BMD measurements. The FRAX tool has limitations in identifying major osteoporotic fractures from any fracture,³⁷ but for the purpose of this study, was used to distinguish high-risk women (with poor bone health) from lower risk women.

In summary, pre-existing osteoporosis is an important comorbidity in women who develop MM, and is associated with a higher risk of MM mortality. Older women and those with low BMI are most likely to have high FRAX scores. Recognizing osteoporosis as a risk factor associated with MM mortality is an important prognostic factor in post-menopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- Osteoporosis is highly prevalent in the aging adult, and very little is known on how this comorbid condition contributes to outcomes in individuals who develop MM.
- Preexisting osteoporosis is an important comorbidity in women who develop MM, and is associated with a higher risk of mortality.
- Recognizing osteoporosis as a risk factor associated with MM mortality is an important prognostic factor in postmenopausal women, especially in older women and individuals with a lower BMI.

Figure 1.

Evaluating Pre-Existing Bone Health in Women Who Develop Multiple Myeloma

Abbreviation: WHI = Women's Health Initiative.

Figure 2.

Associations Between High FRAX Scores, High OST, and Risk of Death. Adjusted Hazard Ratios Estimated From Cox Model With Baseline Hazard Stratified for OS/CT Study and Age (by Year) at Diagnosis (Unadjusted Model HRs) for 362 Participants Who Developed MM. Adjusted HRs Adjustments Further Include: Race, Education, Region, BMI, Menopausal Hormone Use, Baseline Vitamin D Supplementation, Baseline Calcium Supplementation, Rheumatoid Arthritis at Baseline

Abbreviations: BMI = body mass index; CI = confidence interval; CT = clinical trial cohort; FRAX = Fracture Risk Assessment Tool; HR = hazard ratio; MM = multiple myeloma; OS = observational study cohort; OST = Osteoporosis Self-assessment Test.

Table 1

Multiple Myeloma WHI Cohort Participants by FRAX Score (n = 362)

	MM FRAX Low (n = 264), N (%)	MM FRAX High (n = 98), N (%)	P Value ^a
Mean age at screening, y (SD)	63.4 (5.5)	71.6 (4.1)	<.001
50–59	63 (23.9)	0(0)	<.001
60–69	167 (63.3)	29 (29.6)	
70–79	34 (12.9)	69 (70.4)	
Age at MM diagnosis, y	70.7 (6.4)	78.7 (4.7)	<.001
50–69	110 (41.7)	3 (3.1)	<.001
70–75	91 (34.5)	18 (18.4)	
76–90	63 (23.9)	77 (78.6)	
Race			<.001
White	198 (75.0)	93 (94.9)	
Black	50 (18.9)	2 (2.0)	
Other	16 (6.1)	3 (3.1)	
Education			.440
High school or less	91 (34.5)	38 (39.2)	
Some college	101 (38.3)	30 (30.9)	
Post college	72 (27.3)	29 (29.3)	
Region			.053
Northeast	63 (23.9)	27 (27.6)	
South	62 (23.5)	18 (18.4)	
Midwest	70 (26.5)	16 (16.3)	
West	69 (26.1)	37 (37.2)	
Ever hormone use			.350
Never	102 (39.8)	32 (33.0)	
Past	57 (22.3)	28 (28.9)	
Current	97 (37.9)	37 (38.1)	
Mean BMI at baseline (SD)	29.1 (5.9)	25.6 (4.0)	<.001
Under/normal (<25)	65 (24.8)	49 (50.0)	<.001
Overweight (25–30)	107 (40.8)	35 (35.7)	
Obese (≥ 30)	90 (34.4)	14 (14.3)	
Mean physical activity, MET/week (SD)	11.9 (14.9)	14.8 (13.6)	.086
Ever smoker			.904
No	141 (53.8)	51 (54.8)	
Yes	121 (46.4)	42 (45.2)	
Alcohol use			.294
Non-drinker	81 (31.0)	27 (27.8)	
<1 drink a week	87 (33.3)	25 (25.8)	
1–7 drinks a week	63 (24.1)	31 (32.0)	
7+ drinks a week	30 (11.5)	14 (14.4)	
Ever diagnosed with rheumatoid arthritis			.077

	MM FRAX Low (n = 264), N (%)	MM FRAX High (n = 98), N (%)	P Value ^a
No	249 (98.0)	90 (93.8)	
Yes	5 (2.0)	6 (6.3)	
Parental bone fracture			.541
No	145 (58.5)	51 (54.3)	
Yes	103 (41.3)	43 (45.7)	
Ever diagnosed with osteoporosis			.086
No	236 (91.1)	83 (84.7)	
Yes	23 (8.9)	15 (15.3)	
Baseline vitamin D supplementation			.388
No	254 (96.2)	92 (93.9)	
Yes	10 (3.8)	6 (6.1)	
Baseline calcium supplementation			.081
No	215 (81.4)	71 (72.5)	
Yes	49 (18.6)	27 (27.6)	
CAD participant			.999
No	195 (73.9)	72 (73.5)	
Yes	69 (26.1)	26 (26.5)	
HRT participant			.561
No	207 (78.4)	80 (81.6)	
Yes	57 (21.6)	18 (18.4)	
Extension cohort			.279
No	101 (38.3)	44 (44.9)	
Yes	163 (61.7)	54 (55.1)	
Duration between WHI enrollment and MM diagnosis, y			.710
Mean (SD)	7.3 (4.0)	7.1 (3.9)	
Median (range)	7.3 (0.16–15.4)	7.4 (0.04 – 15.7)	

Abbreviations: BMI = body mass index; CAD = cyclophosphamide, adriamycin, and dexamethasone; FRAX = Fracture Risk Assessment Tool; HRT = hormone replacement therapy; MM = multiple myeloma; SD = standard deviation; WHI = Women's Health Initiative.

^aCategorical covariates compared by the Fisher exact test. Continuous covariates compared between high/low baseline FRAX by a 2-sample *t* test, assuming unequal variances.