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Factors associated with vertebral fractures in men treated with androgen deprivation therapy (ADT) for prostate cancer

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Abstract

PURPOSE—Androgen deprivation therapy (ADT) for prostate cancer causes accelerated loss of bone mineral density (BMD) and is associated with increased fracture risk. We evaluated risk factors associated with vertebral fractures among men enrolled in a fracture prevention trial.

MATERIALS & METHODS—Analysis included men receiving ongoing ADT for prostate cancer and enrolled in a phase III fracture prevention trial. All men were either age ≥ 70 years or had low BMD (T-score < −1.5 for the lumbar spine or total hip). We analyzed demographic and laboratory characteristics of those with and without vertebral fractures at the time of study entry.

RESULTS—A total of 162 of the 1,244 subjects (13.0%) had a vertebral fracture at baseline. Two factors were significantly associated with prevalent vertebral fractures: white race ($p = 0.028$ when compared with non-white race) and osteoporosis ($p = 0.002$ for osteoporosis at any site; $p = 0.053$ for osteoporosis at the spine; $p = 0.002$ for osteoporosis at the hip). Lower BMD was also significantly associated with vertebral fractures when analyzed as a continuous variable. Factors not associated with vertebral fractures included age, country of residence, ADT duration at baseline, ADT mode, BMI, testosterone, estradiol, CTX, BSAP, and osteocalcin. Results were similar in analyses limited to men ≥ 70 years old.

CONCLUSIONS—White race and low BMD were significantly associated with vertebral fractures in this study of men treated with ADT for prostate cancer. These observations should inform the assessment of fracture risk in this vulnerable population.

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Keywords

prostate cancer; androgen deprivation therapy; fracture; osteoporosis

Introduction

Fragility fractures are common among men and have the potential to cause considerable morbidity and mortality. Vertebral fractures can cause pain and loss of height. Hip fractures in men can be debilitating and have been associated with mortality rates as high as 37.5%.[1] Among men, the most frequent etiologies of acquired osteoporosis are chronic glucocorticoid treatment, excessive alcohol intake, and hypogonadism.[2]

ADT is a common treatment for prostate cancer and is known to worsen the burden of osteoporosis among men who receive it. ADT drastically lowers both estrogen and testosterone, hormonal changes that cause accelerated loss of bone mineral density[3–7] and are associated with an increased risk for fractures.[8–11]

Low BMD is a broadly-appreciated risk factor for fractures. In the general population, epidemiologic data have been used to identify a number of additional factors that are associated with fragility fractures independent of their effects on BMD. These clinical risk factors include age, low body mass index (BMI), prior fragility fracture, family history of hip fracture, current tobacco smoking, chronic use of glucocorticoids, daily consumption of ≥ 3 units of alcohol, rheumatoid arthritis, and other conditions associated with secondary osteoporosis.[12]

Although large population-based analyses have identified risk factors for fracture in the general population, less is known about risk specifically among men who receive ADT. Risk assessment in this population has historically been driven by BMD measurements. Current National Comprehensive Cancer Network (NCCN) prostate cancer guidelines[13] advocate the use of the World Health Organization/FRAX tool (http://www.shef.ac.uk/FRAX/), a risk prediction algorithm that was developed for the general population. When FRAX is applied to men receiving ADT, it identifies a high proportion of patients who reach accepted osteoporosis treatment thresholds.[14, 15]

The present analysis aims to identify factors associated with prevalent vertebral fractures in a population of men receiving ADT and at elevated risk for fracture due to age and/or BMD. We analyzed baseline characteristics among men enrolled in a phase III fracture-prevention trial. Given that the trial enrolled patients who were age < 70 only if BMD was consistent with osteoporosis, we conducted additional analyses confined to the portion of the cohort that was age ≥ 70.

Materials and Methods

We analyzed baseline data from subjects enrolled in a phase III randomized, double-blind, placebo controlled trial of toremifene to prevent incident fractures in men receiving ADT for prostate cancer. Institutional review board approval was obtained for each site of this multi-centered trial. All participants provided written informed consent with guarantees of confidentiality. Enrollment included men age 50 years or older with histologically documented prostate cancer and serum prostate specific antigen (PSA) 4 ng/ml or less. All men had a history of at least 6 months of continuous gonadotropin releasing hormone (GnRH) agonist treatment, at least 12 months intermittent GnRH agonist treatment, or bilateral orchiectomies.

All subjects were either age ≥ 70 years or had low BMD of the lumbar spine or hip (T-score of < −1.5 for the lumbar spine or total hip). Enrollment criteria excluded men who in the previous 45 days had received oral glucocorticoids, prescription treatment for osteoporosis, or agents that affect testosterone. The study also excluded men with Paget's disease of bone, greater than 4 morphometric vertebral fractures, or any history of thromboembolic disease.

The following baseline information was collected: age, country of residence, race, height, weight, ADT duration, form of ADT, bone mineral density at relevant anatomic sites, testosterone, estradiol, C-telopeptide, bone-specific alkaline phosphatase, osteocalcin, and presence or absence of a prevalent vertebral fracture.

The primary objective of the present analyses was to describe the demographic and laboratory characteristics that were significantly associated with vertebral fractures identified at the time of study entry. As men who were < 70 years old were required to have osteopenia (T-score of < −1.5) at the lumbar spine or total hip, we performed a second set of analyses that were limited to men ≥ 70 years old. These men accounted for approximately 80% of the overall cohort.

Statistical analyses were carried out using the SAS system for statistical analysis version 9.1. Features expressed as continuous data (age, body mass index, bone mineral density of the hip and spine, total testosterone, estradiol, CTX, BSAP and Osteocalcin) were compared between patients with and without prevalent vertebral fractures at baseline using ANCOVA that included country as a covariate. The distribution of categorical features (Age group: ≤ 70 or > 70, Residence: Mexico or USA, Race: White or Other, ADT duration: ≤ 1yr or > 1 yr and ADT mode: GnRH agonist or orchiectomy) were compared between patients with and without prevalent vertebral fractures using the Cochran-Mantel-Hanzel test for general association stratified by country.

Results

These analyses included the baseline data from 1244 subjects in the intention to treat population with available vertebral fracture assessments. A total of 162 subjects (13.0%) had been diagnosed with a vertebral fracture at baseline. Table 1 summarizes the baseline characteristics according to prevalent vertebral fracture.

White race and osteoporosis at any site were significantly ($p = 0.028$ and $p = 0.002$, respectively) associated with prevalent vertebral fractures in the overall cohort (see Table 1). Individually, osteoporosis of the hip was significantly ($p = 0.002$) associated with prevalent vertebral fracture; whereas, osteoporosis of the spine was not ($p = 0.053$). Average BMD of the hip (T-score -1.89 ± 0.08 with fracture, -1.53 ± 0.03 without fracture) and of the spine (T-score -0.87 ± 0.13 with fracture, -0.42 ± 0.05 without fracture) was significantly ($p < 0.001$ and $p = 0.001$, respectively) lower among those patients presenting with a vertebral fracture.

Age was not significantly associated with prevalent vertebral fractures ($p = 0.515$). Notable additional factors not significantly associated with prevalent vertebral fractures included ADT duration at baseline, ADT mode, country of residence, BMI, testosterone, estradiol, CTX, BSAP, and osteocalcin.

The absence of a relationship between age and vertebral fracture might have been due to the requirement that subjects less than 70 years had low BMD. To address this concern, we conducted additional analyses restricted to the 1002 subjects who were greater than or equal to 70 years old. In analyses confined to this group (Table 2), white race and osteoporosis at any site were again significantly ($p = 0.035$ and $p < 0.001$, respectively) associated with

prevalent fractures. Osteoporosis at the spine and at the hip was also significantly ($p = 0.006$ and $p < 0.001$, respectively) associated with vertebral fracture.

Discussion

Prevalent vertebral fractures at the time of enrollment in this phase III trial were common (13.0% in the overall cohort). This is consistent with the design of this fracture-prevention trial as its enrollment criteria included men who were at elevated risk for incident fractures. Though enrollment criteria were different for men age ≥ 70 than men age < 70, prevalent vertebral fractures were similar in the two groups (12.8% among those age ≤ 70, 13.1% among those age ≥ 70).

In this analysis, we found that white race was significantly associated with prevalent vertebral fractures among men treated with ADT. This is consistent with data from the general population.[12] Using population-based FRAX algorithm for residents of the United States, white race confers substantially elevated fracture risk relative to Black, Hispanic or Asian race. The mechanism(s) responsible for these racial differences have not been well defined.

In this analysis, we also found that BMD was significantly associated with prevalent vertebral fractures among men treated with ADT. This, too, is consistent with data from the general population. In one study, for instance, the incidence of vertebral fractures doubled for each standard deviation decrease in lumbar spine or femoral neck BMD.[16] Though the majority of fragility fractures occur in people with non-osteoporotic BMD,[17] BMD is clearly a significant piece of information when risk-stratifying individual patients.

Hip BMD may be the most reliable screening parameter as it is the site most strongly correlated with fractures.[18, 19] Spine BMD can be confounded by focal artifacts due to osteoarthritis-related degenerative changes.[20] These artifacts can falsely elevate the measured BMD and lead to under-estimation of true fracture risk.

Advancing age is independently associated with increased fracture risk in the general population[12] but was not associated with elevated vertebral fracture risk in this analysis. There are several potential reasons for this. First, study enrollment criteria limited the assessment of age as a contributing factor. Men age < 70 were required to have low BMD (T-score < −1.5 at the lumbar spine or total hip). Second, the age range within the cohort was relatively small (76.0 ± 0.2 years). Third, competing risk due to ADT may overwhelm age-related effects.

Population-based data have shown that the relative risk of fracture increases with increasing duration of ADT.[8, 10] Our analysis did not find a significant association between ADT duration and prevalent vertebral fractures. One potential reason for this negative finding is that a large majority of subjects had already received > 1 year of ADT (mean duration at study entry was 4.0 years). The effect of ADT on BMD is most marked in the first year of therapy.[21] The added incremental fracture risk attributable to each subsequent year of therapy during prolonged ADT may be modest.

Though the hormonal environment is clearly an important determinant of BMD and fracture risk, testosterone and estradiol were not significantly associated with vertebral fractures in this analysis. In the general population, estradiol and testosterone are correlated with bone mineral density[22–24] and fracture risk[25–27] in older men. The absence of such an association in our analysis is likely due to the fact that all men were maintained on ADT. Estradiol and testosterone were therefore universally quite low within this cohort. The difference between above-median and below-median testosterone levels is quite small when a large majority of

the subjects have serum total testosterone in the castrate range (<50 ng/dL). Mean estradiol in this study was approximately 12 ng/dL, a level that would have been in the lowest quartile of men in the MrOs Swedish cohort and is correlated with increased fracture risk.[28]

Conclusions

Vertebral fractures cause substantial morbidity and mortality among men treated with ADT for prostate cancer. In this study of men receiving ADT, white race and low BMD were significantly associated with vertebral fractures. These observations should inform the assessment of fracture risk in this vulnerable population.

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Key abbreviations

NOF	National Osteoporosis Foundation
ADT	Androgen deprivation therapy
WHO	World Health Organizationl
BMD	Bone mineral density
BMI	Body Mass Index
GnRH agonist	Gonadotropin releasing hormone agonist
NCCN	National Comprehensive Cancer Network

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TABLE 1

Subject Characteristics by Prevalent Fracture

	No Prevalent Fractures	Prevalent Fractures	
	N (%)Mean ± SD	N (%)Mean ± SD	p-value
Overall cohort	1082 (100%)	162 (100%)	
Age	75.98 ± 0.22	76.41 ± 0.53	0.515
Age			0.960
≤ 70	211 (19.50)	31 (19.14)	
> 70	871 (80.50)	131 (80.86)	
Residence			0.502
Mexico	169 (15.62)	22 (13.58)	
USA	913 (84.38)	140 (86.42)	
Race			0.028
White	768 (70.98)	128 (79.01)	
Other	314 (29.02)	34 (20.99)	
BMI	28.23 ± 0.13	28.15 ± 0.35	0.767
ADT duration at baseline			0.497
<= 1 year	173 (16.62)	22 (14.29)	
> 1 year	868 (83.38)	132 (85.71)	
ADT mode			0.136
GnRH agonist	995 (91.96)	145 (89.51)	
bilateral orchiectomies	87 (8.04)	17 (10.49)	
BMD Hip	−1.53 ± 0.03	−1.89 ± 0.08	<0.001
BMD Spine	−0.42 ± 0.05	−0.87 ± 0.13	0.001
Testosterone	30.72 ± 2.03	27.01 ± 3.78	0.575
Estradiol	12.27 ± 0.25	11.51 ± 0.62	0.246
CTX	0.6 ± 0.01	0.61 ± 0.02	0.672
BSAP	29.5 ± 0.40	29.72 ± 0.74	0.761
Osteocalcin	11.31 ± 0.17	11.45 ± 0.38	0.887

TABLE 2

Baseline Subject Characteristics by Prevalent Fracture, age > 70

	No Prevalent Fractures	Prevalent Fractures	
	N (%)Mean ± SD	N (%)Mean ± SD	p-value
Overall cohort	871 (100%)	131 (100%)	.
Age	78.6 ± 0.17	78.72 ± 0.43	0.853
Residence			0.171
Mexico	125 (14.35)	13 (9.92)	.
USA	746 (85.65)	118 (90.08)	.
Race			0.035
White	635 (72.90)	109 (83.21)	.
Other	236 (27.10)	22 (16.79)	.
BMI	28.15 ± 0.14	28.09 ± 0.40	0.732
ADT duration			0.647
<= 1 year	136 (16.23)	18 (14.40)	.
> 1 year	702 (83.77)	107 (85.60)	.
ADT			0.412
GnRH agonist	801 (91.96)	120 (91.60)	.
bilateral orchiectomies	70 (8.04)	11 (8.40)	.
Testosterone	31.61 ± 2.44	23.47 ± 0.76	0.274
Estradiol	12.17 ± 0.28	11.25 ± 0.65	0.185
Estradiol			0.096
<= median	430 (51.37)	76 (58.46)	.
> median	407 (48.63)	54 (41.54)	.
CTX	0.59 ± 0.01	0.59 ± 0.02	0.997
BSAP	28.93 ± 0.45	29.43 ± 0.82	0.537
Osteocalcin	11.47 ± 0.20	11.77 ± 0.43	0.640