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Incidence and risk factors for low trauma fractures in men with prostate cancer ☆

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ABSTRACT

Background: Men with prostate cancer on androgen deprivation therapy (ADT) are at increased risk of bone loss. The present study sought to determine the incidence of low trauma fracture in men with prostate cancer (PC), and to characterize the association between potential risk factors and fracture risk in these men.
Methods: In the prospective, population-based Dubbo Osteoporosis Epidemiology Study, 43 men aged 60+ years reported a history of prostate cancer; among whom, 22 men received ADT, and 21 men did not. Low-trauma fractures were ascertained between 1989 and 2004. Bone mineral density at the femoral neck (FNBMD), postural instability and lifestyle factors were obtained at baseline.
Results: Men with prostate cancer had significantly higher lumbar spine BMD than those without cancer ($p=0.013$). During the follow-up period, 15 men with prostate cancer had sustained a fracture, yielding the age-adjusted incidence of fracture among this group was 31.6 per 1000 person-years, which was greater than those without cancer (22.1 per 1000 person-years). The age-adjusted incidence of fracture was more pronounced among those with prostate cancer on ADT (40.2 per 1000 person-years). After adjusting for age, the increase in fracture risk among prostate cancer patients was associated with lower femoral neck BMD (hazard ratio [HR] per SD=1.8, 95% CI: 1.0–3.4) and increased rate of bone loss (HR 2.3, 1.2–4.6).
Conclusions: Men with prostate cancer, particularly those treated with ADT, had an increased fracture risk. Although the average BMD in men with prostate cancer was higher than men without cancer, a low BMD prior to treatment or increased rate of bone loss after initiating ADT treatment was each a significant predictor of fracture in these.

Introduction

Prostate cancer is a frequently diagnosed disease among elderly men, and is the second common cause of cancer deaths [1]. In men with generalized disease, androgen deprivation therapy (ADT) following radical prostatectomy may delay tumour progression and improve survival [2]. Moreover, men without metastatic disease and with a lower risk of disease progression are often treated with ADT [3]. Because hypogonadism is a risk factor for secondary osteoporosis and fracture in men [4], and there are indications that men treated with ADT are at increased risk of bone loss and osteoporosis [5–9], the delayed skeletal side effect of androgen deprivation may increase fracture risk in men with prostate cancer.

The incidence of fracture in men with prostate cancer has been reported to be higher in men who have undergone therapeutic orchiectomy than men who have not undergone such treatment [10]. Moreover, medical castration, such as treatment with luteinizing hormone–release hormone (LH–RH) agonist, has been suggested to be a risk factor of fracture [11–14]. Although these studies were retrospective, and only one study reported data from a population-based sample [15], a recent longitudinal register study further supported the conjecture, in which the investigators reported an association between fracture risk and the duration of ADT [16]. However, the incidence of fracture following prostate cancer in men not treated with ADT is still not known.

Low bone mineral density (BMD) is a well-known risk factor of fracture in men [17,18]. Moreover, non-skeletal risk factors, such as postural instability, have been identified to be significant predictors of fracture [19]. However, the relative importance of these risk factors among men with prostate cancer has so far not been evaluated. The present study was therefore designed to determine the incidence of low trauma fracture in men with prostate cancer, and to characterize the association between potential risk factors and fracture risk in a prospective population-based study.

Materials and methods

Study population

The present study was part of the Dubbo Osteoporosis Epidemiology Study (DOES), which was designed as a prospective, population-based epidemiological investigation. The study's main objective was to evaluate risk factors for and outcomes of fractures in elderly men and women [19,20]. In 1989, all men aged 60 or above living in Dubbo were invited to participate in the study. Dubbo is a semi-urban city of approximately 32,000 people 400 km northwest of Sydney, Australia. The city was selected for the study because the age and gender distribution of the population closely resembled the Australian population, and

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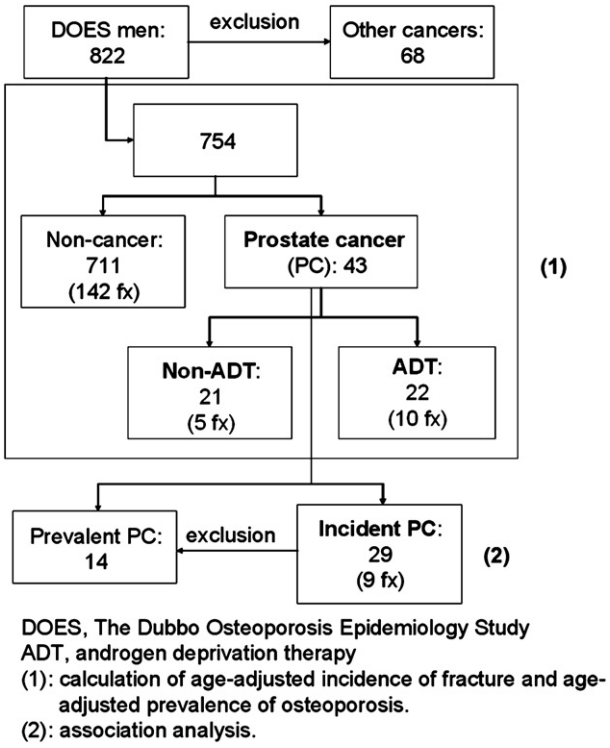

Fig. 1. Data of men with prostate cancer from DOES included in the analysis.

it is relatively isolated in terms of medical care, so that virtually complete ascertainment of all fractures occurring in the target population is possible. From 1989 to 1993, a total of 709 Caucasian males from an initial population of 1960 males were recruited into the study. The study was approved by the St Vincent's Campus Research Ethics Committee and informed written consent was obtained from each participant.

Study sample

Between 1989 and 2004, 43 men were clinically diagnosed to have prostate cancer; among whom, 14 had the disease at the time of study entry and 29 developed incident cancer during the follow-up period (Fig. 1). The year of diagnosis, time of treatment and type of treatment were recorded. The types of treatment were classified into two groups; (1) Androgen deprivation therapy, which included antiandrogens (Androcur), gonadotropin-releasing hormone agonists (Zoladex), estrogens (Stilboestrol), or bilateral orchiectomy and (2) no androgen deprivation therapy included surgical prostatectomy, irradiation-, chemo- or conservative therapy without any concomitant androgen deprivation therapy.

Data collection

All men were interviewed by a nurse coordinator at baseline and subsequently visits which had taken place every two-year interval. Each man was administered a standardized questionnaire to solicit information on general health (history of diseases, use of medications and surgical treatment), anthropometric data (height and weight), lifestyle factors (dietary calcium, past and present tobacco use) and fracture history.

To identify all fractures that occurred in the study population following the baseline measurements, all X-ray reports from the two area radiology services that service the entire Dubbo city were reviewed [19,20]. Vertebral fractures were included only if the clinical history suggested a recent symptomatic fracture and a previous X-ray showed no fracture. Morphometric vertebral fractures were not assessed in this study.

Bone mineral density (BMD, g/cm^2) was measured at the femoral neck (FNBMD) and at the lumbar spine (LSBMD) by DXA using Lunar DPX densitometer (GE-Lunar Corporation, Madison, WI) at each visit. The right hip was scanned in all cases unless there had been a hip replacement or a hip fracture, in which case the left hip was scanned. The radiation dose with this method is <0.1 μGy. The coefficient of variation of BMD in our institution in normal subjects is 1.5% and 2% at the femoral neck and lumbar spine, respectively [21].

Postural instability was assessed by body sway and quadricep strength. Body sway was measured by using a simple sway-meter that measured displacement of the body at the level of the waist with eyes closed standing on high-density foam in 30 s. Quadricep strength (maximum isometric contraction) was measured in the sitting position in the subject's dominant leg with a horizontal spring gauge calibrated to 50 kg force [22].

Statistical analysis

Incidence of fracture was calculated as the number of fracture cases per 1000 person-years. Because the number of fractures was relatively small relative to the population, its incidence was assumed to follow a Poisson distribution, from which the 95% CI of the incidence can be constructed. The incidence was computed by taking into account the age structure of the entire DOES men cohort.

The prevalence of osteoporosis in men with prostate cancer in the study sample was compared with the prevalence of those without cancer in the DOES population with adjustment for age. The rate of change in BMD for each of the two measurement sites was calculated as the relative difference between the base line measurement and the last measurement (prior to the fracture event or at study end), divided by the time between these two visits. The classification of osteoporosis was based on the World Health Organization diagnostic criteria, in which osteoporosis was defined as a FNBMD≥2.5 SD below the young normal mean for men.

In order to assess risk factors of fracture in prostate cancer patients, Cox's proportional hazards regression model [23] was used to estimate relative hazard and 95% confidence interval for each standard deviation (SD) or unit change or in specified groups compared with reference group with categorized risk factors. In this model, the outcomes were the fracture event and time to fracture. The statistical significance of parameter estimates derived from the Cox's model was tested with the likelihood ratio statistics [24]. The proportional hazards assumption in the Cox's regression model was assessed by weight residuals [25]. All database management and statistical analyses were performed via the SAS Statistical Analysis System [26] and R language [27].

Results

Characteristics of men with prostate cancer and those without cancer

Between 1989 and 2004, among 846 men in the DOES study sample, 711 were non-cancer participants, 43 men with prostate cancer and 68 with other cancers (Fig. 1). Baseline clinical characteristics of men with prostate cancer and those without cancer are shown in Table 1. Men with prostate cancer had significantly greater baseline

Table 1
Characteristics of men with prostate cancer and those without cancer

Variables	Non-cancer	Prostate cancer	Standardized difference		*p*-value
	(*n*=711)	(*n*=43)	(95% CI)[a]		
Baseline age (years)	71 (6)	70 (6)	−0.16	(−0.48, 0.15)	0.3098
Age at diagnosis of PC (years)	71 (6)	72 (5)	0.28	(−0.03, 0.58)	0.0795
Height (cm)	173 (7)	172 (6)	−0.14	(−0.46, 0.18)	0.3882
Weight (kg)	78 (13)	80 (12)	0.18	(−0.14, 0.50)	0.2768
Femoral neck BMD (g/cm^2)	0.91 (0.15)	0.94 (0.15)	0.24	(−0.08, 0.57)	0.1412
Rate of change in BMD (%/year)[b]	−0.46 (1.50)	−0.70 (1.13)	−0.16	(−0.56, 0.23)	0.4170
Lumbar spine BMD (g/cm^2)	1.24 (0.21)	1.33 (0.28)	0.41	(0.09, 0.72)	0.0128
Rate of change in BMD (%/year)[b]	0.35 (1.91)	−0.58 (1.94)	−0.49	(−0.89, −0.10)	0.0148
Postural sway (mm^2)[c]	7.00 (1.18)	6.91 (1.23)	−0.07	(−0.39, 0.24)	0.6540
Quadricep strength (kg)[c]	3.39 (0.58)	3.33 (0.62)	−0.10	(−0.43, 0.23)	0.5608
Dietary calcium (mg/day)	629 (342)	681 (370)	0.15	(−0.17, 0.47)	0.3519
Fall in the last 12 months (*n*, %)	140 (19.7)	12 (29.3)	1.69	(0.84, 3.39)	0.1376
Smoking (*n*, %)	444 (62.5)	26 (60.5)	0.92	(0.49, 1.73)	0.7945

Values are mean (SD), unless otherwise specified.
[a] For categorical variables, effect size was shown and using Chi-squared test.
[b] Difference between the baseline measurement and the last measurement prior to fracture or study end, divided by the time between the two measurements.
[c] Values are natural logarithm.

Table 2
Age-adjusted prevalence of osteoporosis and age-adjusted incidence of fracture between men with prostate cancer and those without cancer

	Age-adjusted rate[a]	95% (CI)
Prevalence of osteoporosis		
Non-cancer	14.5	(11.7, 18.0)
Prostate cancer	5.3	(1.3, 21.3)
Incidence of fracture		
Non-cancer	22.1	(18.8, 26.1)
Prostate cancer	31.6	(19.0, 52.4)
Prostate cancer with ADT	40.2	(21.6, 74.8)
Prostate cancer without ADT	22.1	(9.2, 53.1)

ADT, androgen deprivation therapy.
Osteoporosis was based on femoral neck BMD *T*-scores ≤ −2.5.
[a] Rates were adjusted for the Dubbo Osteoporosis Epidemiology Study men sample.

lumbar BMD (0.4SD, *p*-value=0.013) and greater rate of change in lumbar spine BMD than those without cancer (0.5%/year, *p*-value=0.015). However, the difference was not observed at the femoral neck site. There were also no significant differences between the two groups in terms of age, anthropometric measurements, postural sway, fall, daily calcium intake and smoking status.

The age-adjusted prevalence of osteoporosis in men with prostate cancer (5.3%; 95% CI: 1.3–21.3%) was lower than in men in the cohort without cancer (14.5%; 95% CI: 11.7–18.0%) (Table 2).

During the follow-up period (median 11.1 years), 15 prostate cancer patients had sustained at least one low trauma fracture (3 at the vertebrae; 2 at each site of the hip, rib and proximal tibia; and 1 each for the humerus, clavicle, sternum, distal femur, malleolus and hand). The age-adjusted incidence of fracture (per 1000 person-years) in men with prostate cancer was 31.6 (95% CI: 19.0–52.4) which was higher than those in the DOES cohort without cancer (22.1; 95% CI: 18.8–26.1). The age-adjusted incidence of fracture was more pronounced among men with prostate cancer on ADT (40.2; 95% CI: 21.6–74.8). Although men with prostate cancer on ADT had a higher risk of fracture than men with prostate cancer but not on ADT, neither of the observed differences in risk was significant. (Table 2)

Risk factors of fracture

Because 14 of the 43 men were diagnosed with prostate cancer prior to or at the initial visit, baseline characteristics prior to the diagnosis of prostate cancer were analyzed in 29 of the men. Baseline characteristics of prostate cancer patients with and without fracture are shown in Table 3. As expected, men with prostate cancer who sustained a low trauma fracture had significantly lower weight, lower femoral neck BMD and higher rate of bone loss compared to those without fracture. There were no statistically significant differences between those with and without fracture in terms of age, height, postural sway, quadricep strength and lifestyle factors, including daily calcium intake and smoking.

Table 3
Characteristics of men with incident prostate cancer (PC)[a]

	All subjects	Any fracture	Non-fracture	*p*-value
	(*N*=29)	(*N*=9)	(*N*=20)	
Age at diagnosis of PC (years)	71.8 (4.4)	71.2 (5.6)	72.0 (3.9)	0.6664
Height (cm)	172.7 (5.7)	170.2 (4.1)	173.9 (6.0)	0.1135
Weight (kg)	80.6 (11.6)	73.3 (10.0)	83.9 (11.01)	0.0215
Femoral neck BMD (g/cm^2)	0.95 (0.11)	0.89 (0.10)	0.98 (0.11)	0.0477
Rate of change in BMD (%/year)[b]	−0.59 (1.25)	−1.28 (1.20)	−0.30 (1.19)	0.0360
Lumbar spine BMD (g/cm^2)	1.30 (0.24)	1.20 (0.19)	1.34 (0.25)	0.1403
Rate of change in BMD (%/year)[b]	−0.58 (1.93)	−0.75 (1.30)	−0.51 (2.19)	0.7724
Postural sway (mm^2)[c]	6.51 (0.67)	6.80 (0.56)	6.38 (0.69)	0.1148
Quadricep strength (kg)[c]	3.47 (0.32)	3.63 (0.22)	3.40 (0.34)	0.1000
Dietary calcium (mg/day)	622 (299)	549 (360)	655 (271)	0.3866
Fall in the last 12 months (*n*, %)	8 (27.6)	3 (33.3)	5 (25.0)	0.6749[d]
Smoking (*n*, %)	17 (58.6)	5 (55.6)	12 (60.0)	0.8821

Values are mean (SD), unless otherwise specified.
[a] Included men are those with baseline measurements prior to initiation of prostate cancer therapy.
[b] Difference between the baseline measurement and the last measurement prior to fracture or study end, divided by the time between the two measurements.
[c] Values are natural logarithm.
[d] Fisher-exact test.

Table 4
Association between risk factors and fracture among men with prostate cancer

Variable	Unit of comparison	Univariate	Age-adjusted
Age (years)	+4.4	0.88 (0.47, 1.66)	
Weight (kg)	−11	2.27 (0.90, 5.74)	2.25 (0.87, 5.84)
Height (cm)	−6	1.60 (0.76, 3.36)	1.91 (0.80, 4.53)
FNBMD (g/cm^2)	−0.11	1.72 (1.00, 3.13)	1.78 (0.98, 3.37)
FNBMD change (%/year)	−1	2.38 (1.22, 4.63)	2.33 (1.18, 4.60)
LSBMD (g/cm^2)	−0.24	1.49 (0.72, 3.10)	1.47 (0.70, 3.11)
LSBMD change (%/year)	−1	1.29 (0.89, 1.88)	1.31 (0.88, 1.93)
Postural sway (mm^2)[a]	+0.7	1.98 (0.88, 4.44)	2.04 (0.90, 4.64)
Quadricep strength (kg)[a]	−0.3	0.42 (0.15, 1.17)	0.35 (0.10, 1.16)
Androgen therapy	Yes	1.26 (0.31, 5.12)	1.52 (0.33, 7.10)
Daily calcium intake (mg/day)	−300	1.55 (0.68, 3.50)	1.55 (0.68, 3.53)
Fall in the last 12 months	Yes	1.34 (0.33, 5.37)	1.35 (0.34, 5.42)
Smoking	Yes	1.19 (0.32, 4.49)	1.16 (0.31, 4.39)

Values are hazard ratio and 95% confidence interval.
[a] Values are natural logarithm.

Results of the Cox's proportional hazards model suggested that lower femoral neck BMD and higher rate of BMD loss were independently associated with increased fracture risk. Each SD lower in femoral neck BMD was associated with 1.7-fold (95% CI: 1.0–3.1) increase in fracture risk, and each SD higher femoral neck BMD loss was associated with an increase in fracture risk of 2.4-fold (95% CI: 1.2–4.6). After adjusting for age, the two factors remained statistically significant (Table 4).

Discussion

One of the most frequently mentioned conjectures on the side effect of androgen deprivation therapy is that the therapy increases bone loss and fracture risk. In a population-based sample of men aged 60+ with prostate cancer, fracture risk was significantly higher than that in the background population, and this incremental risk was predominantly observed among men on ADT. Results of this prospective study partially support that conjecture. Although men with prostate cancer had a higher femoral neck BMD than the background population, a low femoral neck BMD or increased femoral neck BMD loss was each a significant predictor of fracture.

It is interesting to observe that in the present study, men with prostate cancer had greater level of BMD, especially at the lumbar spine, compared to those without cancer. This difference was consistent with the fact that the age-adjusted prevalence of osteoporosis in prostate cancer men was lower than that in men without cancer. The prevalence of osteoporosis in the present study was comparable to that of previous reports [9,28].

Although it is not clear what factors were responsible for the higher level of BMD among men with prostate cancer, it has been suggested that the difference could be mediated via serum testosterone which seemed to be higher in men with prostate cancer patients [29,30]. However, many longitudinal studies have reported that serum testosterone was either not associated or inversely associated with an increased risk of prostate cancer [31–36]. Moreover, in our recently publication, we have found that there was no significant association between serum testosterone and BMD in Dubbo men [37]. Therefore, it seems that testosterone could not account for the high BMD in men with prostate cancer.

The increased fracture risk in men with prostate cancer has so far predominantly been attributed to ADT [38]. Indeed, the increased fracture risk among men on ADT in this study was about the same

magnitude as previously reported in a large unselected sample of men with bilateral orchiectomy [15]. However, some considerations at the cellular level must also be considered. Prostate cancer cells are known to interfere with physiological bone remodelling, and to produce osteoblastic bone lesions with reduced bone strength. Furthermore, an increase in localised osteoblastic activity might, because of calcium entrapment in bone, induce secondary hyperparathyroidism, with a generalized increased bone resorption [39]. Accordingly, men with prostate cancer not on ADT might also be considered a specific risk group of fracture.

In the present study, in addition to baseline BMD, the rate of BMD loss at the femoral neck was also a significant predictor of fracture. Whether this increased bone loss in fracture men is attributable to ADT or not could not be determined in this study, because of the small sample size. The present finding has important clinical implication, because it suggests that longitudinal measurement of bone mineral density might be a helpful tool in the assessment of fracture risk in men with prostate cancer. In the present study, there was no significant association between rate of change in BMD at the lumbar spine and fracture risk in men with prostate cancer. This lack of association could be due to degenerative changes, such as osteophytosis, that is known to artificially elevate BMD, especially in men [40].

Advancing age, lower weight and higher postural instability were previously shown to be independent risk factors for fracture in men without prostate cancer [19]. Similar trends were observed in the present study, albeit not statistically significant. This is likely due to the small sample size, making the lack of statistical power to detect the significant differences.

The population-based study design allows comparisons of incidence with the underlying population and thereby the results have higher epidemiologic value and clinical relevance. The system of fracture ascertainment included virtually all fractures that allow the study to accurately and reliably define the type and cause of the fracture. However, important limitations should also be considered in interpreting these results. The assessment of prostate cancer event was based on interview and no information on stage, Gleason score or PSA level was obtained. However, none of these parameters has, to our knowledge, previously been shown to be associated with fracture risk. Furthermore, the sample size of men with prostate cancer in this study was modest which could limit the statistical power to detect a modest association.

In summary, men with prostate cancer, particularly those treated with androgen deprivation therapy, had an increased risk of fracture, due partly to lower bone mineral density and increased bone loss. As the number of men with prostate cancer is increasing in the elderly population, the burden of skeletal side effects of the disease and its therapy may increase. Therefore, the identification of risk factors of fracture in men with prostate cancer is an important issue.

Conflict of interest

Dr John Eisman serves as a consultant and receives corporate appointment from Amgen, deCode, Eli Lilly and Company, GE-Lunar, Merck Sharp & Dohme Ltd., Novartis, Organon, Roche-GSK, Sanofi-Aventis and Servier. All other authors have no conflict of interest.

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