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ORIGINAL ARTICLE

Patients with prostate cancer and androgen deprivation therapy have increased risk of fractures—a study from the fractures and fall injuries in the elderly cohort (FRAILCO)

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Abstract

Summary Osteoporosis is a common complication of androgen deprivation therapy (ADT). In this large Swedish cohort study consisting of a total of nearly 180,000 older men, we found that those with prostate cancer and ADT have a significantly increased risk of future osteoporotic fractures.

Introduction Androgen deprivation therapy (ADT) in patients with prostate cancer is associated to increased risk of fractures. In this study, we investigated the relationship between ADT in patients with prostate cancer and the risk of incident fractures and non-skeletal fall injuries both compared to those without ADT and compared to patients without prostate cancer.

Methods We included 179,744 men (79.1 ± 7.9 years (mean ± SD)) from the Swedish registry to which national directories were linked in order to study associations regarding fractures, fall injuries, morbidity, mortality and medications. We identified 159,662 men without prostate cancer, 6954 with prostate cancer and current ADT and 13,128 men with prostate cancer without ADT. During a follow-up of approximately 270,300 patient-years, we identified 10,916 incident fractures including 4860 hip fractures.

Results In multivariable Cox regression analyses and compared to men without prostate cancer, those with prostate cancer and ADT had increased risk of any fracture (HR 95% CI 1.40 (1.28–1.53)), hip fracture (1.38 (1.20–1.58)) and MOF (1.44 (1.28–1.61)) but not of non-skeletal fall injury (1.01 (0.90–1.13)). Patients with prostate cancer without ADT did not have increased risk of any fracture (0.97 (0.90–1.05)), hip fracture (0.95 (0.84–1.07)), MOF (1.01 (0.92–1.12)) and had decreased risk of non-skeletal fall injury (0.84 (0.77–0.92)).

Conclusions Patients with prostate cancer and ADT is a fragile patient group with substantially increased risk of osteoporotic fractures both compared to patients without prostate cancer and compared to those with prostate cancer without ADT. We believe that this must be taken in consideration in all patients with prostate cancer already at the initiation of ADT.

Keywords Androgen deprivation therapy · Fall injuries · Fractures · Prostate cancer

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Introduction

There is continuing evidence that men, although presenting with apparent risk factors for osteoporotic fractures such as previous fragility fractures or treatment with glucocorticoids, are not evaluated properly or treated for osteoporosis to the same extent as women [1, 2]. Although the life-time risk of sustaining a fragility fracture is lower in men than in women [3], the male life expectancy is constantly increasing [4] which is expected to result in increased fracture burden in the future. Furthermore, male patients appear to remain at higher risk of mortality following an index hip fracture both in short- and long-term studies [5].

One large male high-risk group that could easily be detected are those with prostate cancer and androgen deprivation therapy (ADT). Prostate cancer is indeed the most frequently diagnosed malignancy in men [6] and the majority are diagnosed in developed countries [7]. ADT as a treatment of metastatic prostate cancer has been increasing over time [8] and may include gonadotropin-releasing hormone (GnRH) analogues, androgen receptor blockers or a combination of the two. The effects of ADT are mediated through suppression of testosterone to castrate levels which further leads low levels of oestrogen and a state of severe hypogonadism. Indeed, the low serum oestrogen in hypogonadal men seems to have an effect on bone density, comparable with that for postmenopausal women [9]. Studies have shown that hypogonadism together with alcohol abuse and glucocorticoid excess are the most common causes of male osteoporosis [10]. A recently published meta-analysis confirmed that patients with prostate cancer and ADT have a high prevalence of osteoporosis [11], and similar to glucocorticoids, there is a rapid bone loss during the first 6–12 months of therapy [12]. This indicates the importance of identifying and risk-evaluating these patients at an early stage, probably as a routine already when considering ADT.

The relationship between treatment with ADT and increased risk of osteoporotic fractures was initially published more than 20 years ago [13] and subsequently confirmed by several studies [14–18]. However, large studies where patients are compared to the normal population and where adjustment has been made for traditional risk factors for fragility fractures included in fracture risk assessment tools (such as FRAX [19]) are missing.

Therefore, the aim of this study was to investigate the relationship between ADT in patients with prostate cancer and the risk of incident fractures compared to patients without prostate cancer and compared to those with prostate cancer but without ADT, adjusted for traditional risk factures for osteoporotic fractures including the risk of falling.

Methods

Study design

We included a total of 179,744 men (79.1 ± 7.9 years (mean ± SD)) from the recently collected "Fractures and fall injuries in the elderly cohort" (FRAILCO) which is a patient-based cohort study where Swedish national directories are linked in order to study associations regarding fractures, fall injuries, morbidity, mortality, and medications [20–22]. The cohort was collected between 2008 and 2014 to the Swedish national directory "Senior Alert" [23], and the included individuals were followed from the time of registration until death, emigration, or at the end of 2014. The directory was originally designed to serve as a quality registry to support improvements in preventive care for older adults and includes over 20% of the entire Swedish population in this age group. Swedish citizens, 65 years or older were registered in connection to a visit to a healthcare facility by a licenced allied health professional, regardless of diagnosis, comorbidities, functioning, and health. In the end of 2014, more than 90% of all municipalities in Sweden were linked to Senior Alert, and all participants were registered with information about age, sex, height and weight along with several parameters related to the risk of falling, pressure ulcers and nutrition. Information concerning medications, diagnoses, fall injuries, fractures and deaths, in relation to time of registration, were collected using the Drug Dispensation Register (2005–2014), the Patient Register (2001–2014 for outpatient visits and 1987–2014 for admitted patients) and Cause of Death Register. Information regarding immigration and emigration was included from Statistics Sweden. The study was approved by the regional ethical review board in Gothenburg.

Definition of patient groups

The study population of the present study is presented in Fig. 1. Patients were defined as having prostate cancer if they had received ICD code C61 in the Patient register which includes all admitted patients between 1987 and 2014 and all outpatient visits between 2001 and 2014. We further defined patients with prostate cancer as having received ADT if they had any previous prescriptions of a GnRH-agonist with a treatment period of at least 3 months and no more than 1 year since the last dose in the Drug dispensation register (2005–2014). Usage of antiandrogen, alendronate or calcium + vitamin D supplements was defined as any previous prescription of the drug in the register. No information regarding surgical orchidectomy, radiation therapy, Gleason score or presence of skeletal metastases was available in the investigated databases. Patients with prescriptions of GnRH-agonist but without a diagnosis of prostate cancer ($n = 2287$) were excluded from the study cohort.

Definition of outcomes

Fracture information was collected from the National Patient Register, and all non-malignant fracture diagnoses (apart from head fractures) regardless of type of trauma were included. Incident hip fracture was defined as a fractured femoral head, neck, trochanter or subtrochanteric part of femur that occurred after the registration in Senior Alert and that was accompanied with a code for surgical procedure (ICD: S720-S722 in combination with surgical procedure starting with NFB or NFJ39-NFJ99). Incident major osteoporotic fracture (MOF) was defined as a fracture of the hip, vertebrae, upper- or lower arm (S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10,

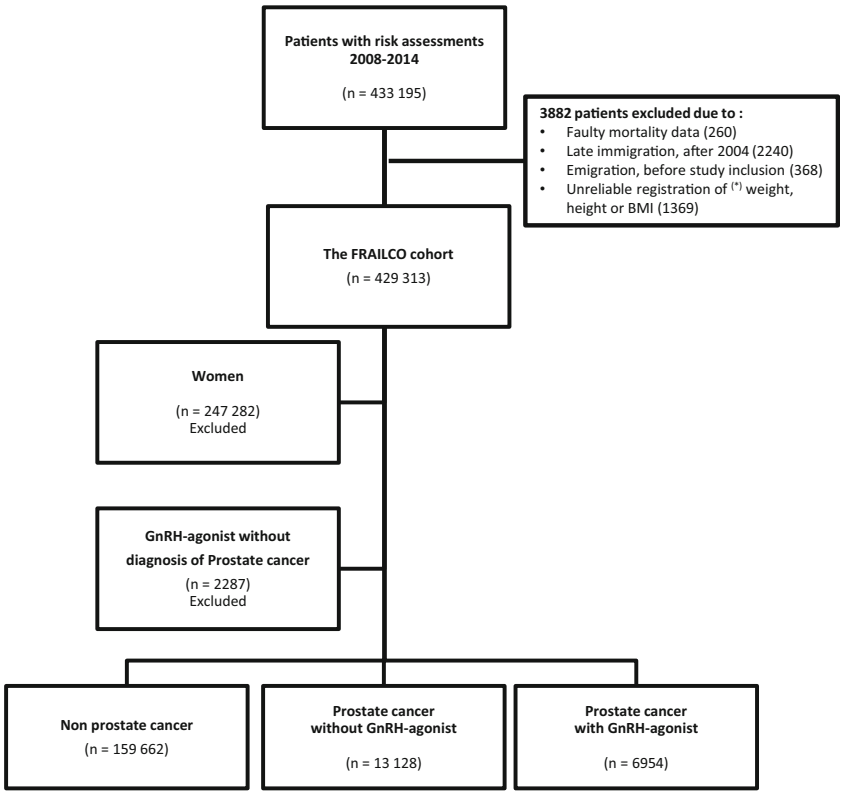

Fig. 1 Flow chart of the entire cohort. Asterisk indicates accepted values after exclusion of top and bottom 1‰ were weight, 30–176 kg; height, 114–197 cm and BMI, 12,23–73,05 kg/m^2

T12, T142, M485). To further ascertain that the defined codes represented an incident fracture and not a previous fracture with a revisit; the second fracture was discarded if the codes were repeated within 5 months. Incident non-skeletal fall injury was classified as any injury (except fractures) occurring after the time of inclusion, that was accompanied by a code representing a fall (S00-T14 (except S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T142, M485) + code representing a fall (W00-W19)).

Definition of traditional risk factors for fracture

Age, weight and height were registered in all patients at inclusion in Senior Alert. We did not have information regarding smoking status in the databases. Previous fracture was defined as any previous diagnosis of a prior fracture according to ICD-codes stated in previous section and rheumatoid arthritis as the presence of the diagnosis according to ICD-codes M05-06. Previous glucocorticoid treatment was defined as any previous period the patient had retrieved prescriptions for more than 450 mg of prednisolone or equivalents over a period of 3 months or more, a dose corresponding to a daily treatment of at least 5 mg prednisolone for 3 months. Secondary osteoporosis was defined as the presence of diagnoses of insulin-dependent diabetes (E10), hyperthyroidism (E05), hypogonadism (E28-29), malnutrition (E40-46), osteogenesis imperfecta (Q780) or chronic liver disease (K70-77). Overconsumption of alcohol was estimated according to several diagnoses of alcohol abuse together with alcohol-related diseases according to ICD-codes (F10, G312, G621, G721, I426, K292, K70, K852, K860, T51, Y912, Y913). We did not have any measurements of bone mineral density in the databases, and the diagnosis of osteoporosis is very rare in the Patient Registry and could not be reliably studied.

Definition of comorbidities and general health

For some analyses, Charlson comorbidity index [24] was used to quantify comorbidity. The index was calculated as a weighted sum of the following diseases: One point each for dementia (F00-F03), ischemic heart disease (I20-I25), congestive heart failure (I50), cerebrovascular disease (I60-I69), disease of arteries, arterioles and capillaries (I70-I79), chronic pulmonary disease (J43-J46), chronic liver disease (K70-K77); one point for mild renal failure (N17-N19) and an extra point if moderate or severe renal failure (N182-N185); one point for diabetes (E10-14) and an extra point if diabetes with end organ damage (E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, H360, H360A, H360B, H360X); two points each for hemiplegia (G81), peptic ulcer disease (K25-K27), tumour without metastasis (C00-C76, C80, C97),

Table 1 Clinical characteristics of the cohort

	Patients without prostate cancer ($n = 159,662$)	Prostate cancer without ADT ($n = 13,128$)	Prostate cancer with ADT ($n = 6954$)
Age, years (mean ± SD)	79 ± 8.0	79 ± 7.4	82 ± 7.0
BMI kg/m^2 (mean ± SD)	26 ± 4.6	26 ± 4.2	25 ± 4.3
Follow-up time, years (median; IQR)	1.3 (0.5–2.3)	1.3 (0.5–2.3)	0.8 (0.3–1.7)
General health description			
General condition (good or fairly good)	142,822 (90%)	11,860 (91%)	5916 (86%)
Nutrition (3/4 portion or more)	135,822 (86%)	11,146 (85%)	5353 (78%)
Drinking (> 700 ml/day)	146,157 (92%)	12,134 (93%)	6210 (90%)
Inclusion site			
Hospital	111,608 (70%)	10,196 (78%)	4863 (70%)
Nursing home	30,146 (19%)	1630 (12%)	1135 (16%)
Residential home service	7548 (4.7%)	534 (4.1%)	486 (7.0%)
Primary care centre	5659 (3.5%)	447 (3.4%)	244 (3.5%)
Rehab unit	4664 (2.9%)	321 (2.4%)	224 (3.2%)
Previous events			
Any fracture	35,731 (22%)	2736 (21%)	1844 (27%)
Hip fracture	9002 (5.6%)	593 (4.5%)	485 (7.0%)
Major osteoporotic fracture	18,906 (12%)	1426 (11%)	1054 (15%)
Comorbidities			
Rheumatoid arthritis	2749 (1.7%)	219 (1.7%)	85 (1.2%)
Dementia	14,435 (9.0%)	1127 (8.6%)	620 (8.9%)
Neurological diseases	49,742 (31%)	4931 (38%)	2442 (35%)
Hypertension	70,783 (44%)	7232 (55%)	3797 (55%)
Ischaemic heart disease	44,896 (28%)	4251 (32%)	2379 (34%)
Heart arrhythmias	44,340 (28%)	4211 (32%)	3281 (34%)
Congestive heart failure	29,576 (19%)	2586 (20%)	1603 (23%)
Stroke	27,696 (17%)	2313 (18%)	1206 (17%)
Chronic obstr. pulmonary disease	13,441 (8.4%)	1136 (8.7%)	633 (9.1%)
Chronic liver disease	2244 (1.4%)	150 (1.1%)	67 (1.0%)
Renal failure	13,229 (8.3%)	1323 (10%)	836 (12%)
Type 2 diabetes	34,559 (22%)	2371 (18%)	1332 (19%)
Medications			
Glucocorticoids	17,076 (11%)	1564 (12%)	1365 (20%)
Alendronate	4951 (3.1%)	462 (3.5%)	282 (4.1%)
Calcium + vitamin D	9401 (5.9%)	868 (6.6%)	765 (11%)
Antiandrogen	684 (0.4%)	3122 (24%)	5371 (77%)

lymphoma or leukaemia (C81-C96) and six points for metastatic solid tumour (C77-C79). From the senior alert questionnaire, 98.9% of the registered individuals provided information regarding previous known falls (yes/no) which was used as a surrogate marker for risk of falling. Characterisation of general condition, food and liquid intake at the time of risk assessment was performed using questions from the validated RAPS or Norton scales [25] used in Senior Alert for risk assessment of decubitus ulcers.

Statistical analysis

Age and BMI are presented as mean ± SD, follow-up time and time since diagnosis of prostate cancer as median (inter-quartile range) and all comorbidities as proportions. We used Cox proportional-hazards models to calculate hazard ratios for associations between the different groups and the outcomes. The follow-up time to fracture was censored for death, emigration or end of study period. In the final multivariable models, estimated

Table 2 Incident events in the cohort

	Patients without prostate cancer	Prostate cancer				
		without ADT	*p* value	with ADT	*p* value**	*p* value***
Patients–no.	159,662	13,128		6954		
Time at risk, days–median (IQR)	463 (190–833)	469 (196–843)		279 (95–614)		
Total follow-up time–patient-years	242,159	20,246		7721		
Any fracture–no. (%)	9644 (6.0%)	732 (5.6%)	0.032	540 (7.8%)	< 0.001	< 0.001
Any fracture/1000 patient-years	42	37		74		
Hip fracture–no. (%)	4293 (2.7%)	322 (2.5%)	0.110	245 (3.5%)	< 0.001	< 0.001
Hip fracture/1000 patient-years	18	16		32		
MOF–no. (%)	5663 (3.5%)	455 (3.5%)	0.656	333 (4.8%)	< 0.001	< 0.001
MOF/1000 patient-years	24	23		45		
Non-skeletal fall injury–no. (%)	7102 (4.4%)	552 (4.2%)	0.201	320 (4.6%)	0.535	0.190
Non-skeletal fall injury/1000 patient-years	30	28		43		
Death–no. (%)	54,723 (34%)	4152 (32%)	< 0.001	4086 (59%)	< 0.001	< 0.001

**Compared to patients without prostate cancer; ***Compared to patients with prostate cancer without ADT

available "traditional risk factors" (age, height, weight, previous fracture, glucocorticoid use, rheumatoid arthritis secondary osteoporosis and estimated over-consumption of alcohol) were forced in to the models together with Charlson comorbidity index, Alendronate, Calcium + vitamin D and self-reported risk of falling (previous fall yes/no in the Senior Alert questionnaire). Within the separate patient groups, we performed another Cox proportional-hazards model where traditional risk factors including calcium-vit D, Charlson comorbidity index and self-reported risk of falling were forced into the model.

An extension of Poisson regression models [26] was used to study the association between potential predictors and the future risk of fracture. All associations were adjusted for age and time since baseline. In contrast to logistic regression, the Poisson regression uses the length of each individual's follow-up period and the hazard function is assumed to be exp. ($\beta_0 + \beta_1$ current time from baseline + β_2 current age + β_3 variable of interest). The observation period of each participant was divided into intervals of 1 month. One fracture per person and time to the first fracture were counted, and time at risk was censored at the time of first fracture, loss to follow-up, death or end of follow-up. Since the current time, since baseline and current age are used in the model, i.e. the age at each time of follow-up, not the age at baseline, the model is taking care of competing risk.

The association between predictive factors and risk of fracture is described as a hazard ratio (HR) per 1 unit change in predictor together with 95% confidence intervals (CI). A two-sided *p* value was used for all analyses and $p < 0.05$ was considered to be significant.

Results

Baseline characteristics

In total, we identified 159,662 patients without prostate cancer and 20,082 patients with prostate cancer. Among those with prostate cancer, 6954 patients were treated with ADT and 13,128 were not. In patients with ADT, the median treatment time with GnRH-agonist was 3.7 years (inter-quartile range 1.7–6.0), and more than 90% of the patients had been prescribed their last dose within 3 months.

The median (inter-quartile range) time since diagnosis of prostate cancer was similar in those with ADT (16 years (8.6–22)) compared to those without ADT (16 years (8.3–22)).

Baseline characteristics of all patient groups are presented in Table 1. In summary, patients with ADT were older, had lower BMI and a shorter follow-up time compared to the other groups. Furthermore, ADT was associated to a larger proportion of patients considered as in poorer general condition at inclusion, and a larger proportion of patients had deficiencies in nutrition- and drinking status. Regarding comorbidities, patients with ADT had a larger proportion of patients with ischemic heart disease, heart arrhythmias, congestive heart failure, and renal failure compared to patients without ADT and compared to patients without prostate cancer.

At inclusion in the registry, patients with ADT had suffered from more previous fractures (any fracture, hip fracture or MOF) compared to all other patients.

Seventy-seven percent of the patients with ADT had been prescribed antiandrogen, and 20% had received per oral glucocorticoid therapy > 3 months in comparison to 12% in all

Table 3 Hazard ratios for patients with prostate cancer compared to patients without prostate cancer

	Patients without prostate cancer ($n = 159,662$)	Prostate cancer					
		Without ADT ($n = 13,128$)		With ADT ($n = 6954$)			
		Compared to patients without prostate cancer	p value	Compared to patients without prostate cancer	p value	Compared to patients with prostate cancer without ADT	p value
Any fracture (HR (95% CI))							
Age, height, weight	Reference	0.94 (0.87–1.01)	0.111	1.46 (1.34–1.59)	< 0.001	1.51 (1.35–1.70)	< 0.001
Traditional risk factors*	Reference	0.96 (0.89–1.04)	0.322	1.42 (1.30–1.54)	< 0.001	1.44 (1.2748–1.61)	< 0.001
Multivariate**	Reference	0.97 (0.90–1.05)	0.449	1.40 (1.28–1.53)	< 0.001	1.34 (1.19–1.50)	< 0.001
MOF (HR (95% CI))							
Age, height, weight	Reference	1.02 (0.92–1.12)	0.756	1.55 (1.39–1.73)	< 0.001	1.50 (1.30–1.73)	< 0.001
Traditional risk factors*	Reference	1.03 (0.94–1.14)	0.514	1.51 (1 35–1 69)	< 0.001	1.44 (1.24–1.66)	< 0.001
Multivariate**	Reference	1.01 (0.92–1.12)	0.802	1.44 (1.28–1.61)	< 0.001	1.34 (1.16–1.56)	< 0.001
Hip fracture (HR (95% CI))							
Age, height, weight	Reference	0.96 (0.86–1.08)	0.519	1.48 (1 30–1 69)	< 0.001	1.51 (1.28–1.79)	< 0.001
Traditional risk factors*	Reference	0.97 (0.87–1.09)	0.642	1.46 (1.28–1.66)	< 0.001	1.46 (1.24–1.74)	< 0.001
Multivariate**	Reference	0.95 (0.84–1.07)	0.355	1.38 (1.20–1.58)	< 0.001	1.38 (1.16–1.65)	< 0.001
Non-skeletal fall injury (HR (95%CI))							
Age, height, weight	Reference	0.96 (0.88–1.05)	0.332	1.20 (1.07–1.34)	0.001	1.21 (1.05–1.40)	0.007
Age, height, weight and Charlson	Reference	0.84 (0.77–0.92)	< 0.001	1.01 (0.90–1.13)	0.920	1.15 (1.00–1.32)	0.057

*Previous fracture, glucocorticoid use, rheumatoid arthritis, estimated over consumption of alcohol, and secondary osteoporosis

**Previous fracture, glucocorticoid use, rheumatoid arthritis, estimated over consumption of alcohol, secondary osteoporosis, Charlson, alendronate, calcium + vitamin D and previous known fall (yes/no)

other patients with prostate cancer and 11% of those without prostate cancer. Only 4.1% of the patients with ADT had ever been prescribed alendronate, compared to 3.5% of patient with prostate cancer but without ADT and 3.1% in patients without prostate cancer. Other osteoporosis drugs were extremely rare and are not presented in patient characteristics.

Incident events

Among patients with prostate cancer and ADT, 59% died during follow-up compared to 32% of all other patients with prostate cancer and 34% of those without prostate cancer. ADT was related to higher rates of any incident fracture, hip fracture and MOF compared to all other patients (Table 2). The rates for hip fracture and MOF per 1000 patient-years were 32 and 45 in patients with ADT compared to 16 and 23 in those with prostate cancer but without ADT and 18 and 24 in patients without prostate cancer.

The crude and adjusted hazard ratios for risk of fractures in prostate cancer patients compared to patients without prostate cancer are presented in Table 3. In summary, patients with ADT had increased risk of any fracture (adjusted HR 95% CI 1.40 (1.28–1.53)), hip fracture (1.38 (1.20–1.58)) and of MOF (1.44 (1.28–1.61)) compared to patients without prostate cancer. In comparison to patients with prostate cancer but without ADT, patients with ADT had increased risk of any fracture (adjusted HR 95% CI 1.34 (1.19–1.50)), hip fracture (1.38 (1.16–1.65)) and of MOF (1.34 (1.16–1.56)). The adjusted survival curves for hip fracture and MOF in patients with prostate cancer and ADT compared to patients without prostate cancer are presented in Fig. 2a, b.

In a Cox-regression analysis adjusted for age, weight, height and Charlson comorbidity index, treatment with ADT was not significantly associated to incident risk of non-skeletal fall injury compared to those without ADT (1.15 (1.00–1.32) or compared to those without prostate cancer (1.01 (0.90–1.13).

Among patients with prostate cancer, known prescription of antiandrogens where related to any incident fracture in a model adjusted for age and BMI (HR 95% CI 1.27 (1.14–1.42). When the variable GnRH-agonists (current ADT) was entered into the model, the relationship between antiandrogens and the outcome was no longer significant (1.08 (0.95–1.22).

Analysis of competing risk

An extension of Poisson regression models was used to study the association between potential predictors and the future risk

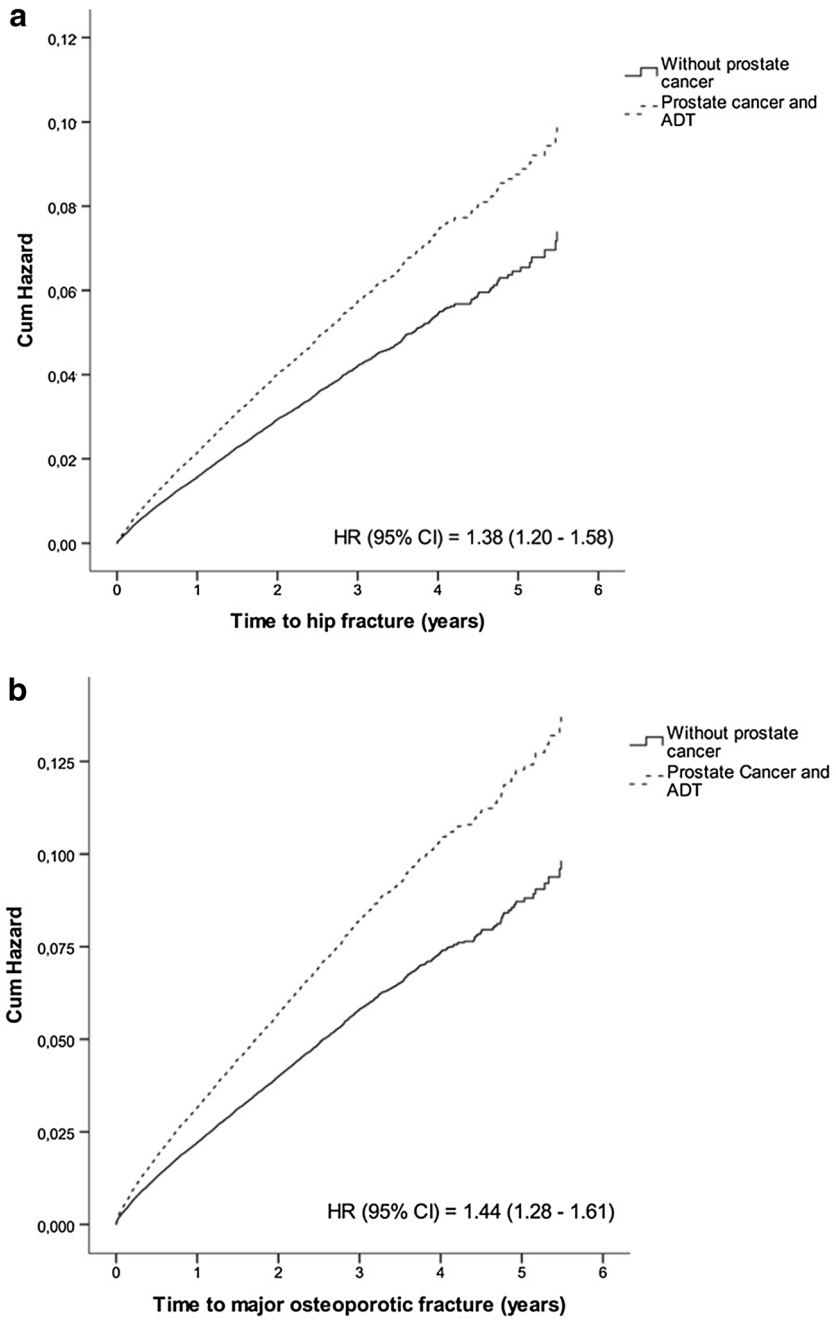

Fig. 2 Survival curves of time to hip fracture (**a**) and major osteoporotic fracture (**b**) in patients with prostate cancer and GnRH-agonist compared to patients without prostate cancer

of fracture. The current time since baseline was used in the model, i.e. the age at each time of follow-up, not the age at baseline, thus the model was taking care of competing risk. In these models, there was no relevant interaction between time since baseline and risk of the outcomes in any of the patient groups. However, we found a significant interaction between age and risk of fracture where the differences in risk were larger in younger patients. This was most evident among young patients with prostate cancer with and without ADT. From the models, hazard ratios according to specified ages (70, 80 and 90 years) were calculated and are presented in Table 4.

Risk factors models within the patient groups

Within the three groups of patients, we performed Cox proportional-hazards models where "traditional risk factors" were forced together including known prescription of calcium/vitamin D, Charlson comorbidity index and self-reported history of falling. The final models are presented in Table 5. The pattern of importance among the selected risk factors was similar in all groups where age, low BMI, previous fracture and previous falls remained highly significant in all patient groups.

Table 4 Crude hazard ratios (95% CI) shown for ages 70, 80 and 90 years in the patient groups according to a Poisson regression model

Current age (year)	Prostate cancer without ADT vs. no prostate cancer	Prostate cancer withADT vs. no prostate cancer	Prostate cancer with ADT vs. prostate cancer without ADT
Any fracture	Interaction term $p < 0.001$	Interaction term $p = 0.12$	Interaction term $p < 0.001$
70	0.63 (0.53, 0.75)*	1.66 (1.33, 2.07)*	2.63 (1.99, 3.48)*
80	0.83 (0.75, 0.93)*	1.49 (1.31, 1.71)*	1.79 (1.50, 2.13)*
90	1.11 (0.97, 1.26)	1.35 (1.16, 1.56)*	1.22 (1.00, 1.48)*
Hip fracture	Interaction term $p < 0.001$	Interaction term $p = 0.006$	Interaction term $p < 0.001$
70	0.55 (0.41, 0.74)*	2.15 (1.53, 3.02)*	3.89 (2.51, 6.02)*
80	0.80 (0.66, 0.96)*	1.63 (1.33, 1.99)*	2.04 (1.56, 2.67)*
90	1.15 (0.95, 1.39)	1.23 (0.99, 1.53)	1.07 (0.81, 1.42)
MOF	Interaction term $p < 0.001$	Interaction term $p = 0.005$	Interaction term $p < 0.001$
70	0.70 (0.56, 0.88)*	2.09 (1.58, 2.77)*	2.99 (2.09, 4.26)*
80	0.93 (0.80, 1.08)	1.64 (1.39, 1.95)*	1.76 (1.41, 2.20)*
90	1.24 (1.05, 1.46)*	1.29 (1.07, 1.56)*	1.04 (0.82, 1.33)
Non-skeletal fall injury	Interaction term $p < 0.001$	Interaction term $p > 0.30$	Interaction term $p = 0.12$
70	0.71 (0.58, 0.86)*	0.97 (0.72, 1.31)	1.38 (0.98, 1.95)
80	0.88 (0.77, 1.01)	1.03 (0.86, 1.24)	1.17 (0.94, 1.45)
90	1.11 (0.94, 1.30)	1.10 (0.90, 1.33)	0.99 (0.78, 1.26)

*$p < 0.001$. An extension of Poisson regression models was used to study the association between potential predictors and the future risk of fracture. The observation period of each participant was divided into intervals of 1 month. One fracture per person and time to the first fracture were counted, and time at risk was censored at the time of first fracture, loss to follow-up, death or end of follow-up. Since the current time, since baseline and current age are used in the model i.e. the age at each time of follow up, not the age at baseline, the model is taking care of competing risk. The association between predictive factors and risk of fracture is described as a hazard ratio (HR) at baseline of the study, per 1 unit change in predictor together with 95% confidence intervals (CI)

Discussion

In this large Swedish cohort of elderly male patients, we found that patients with prostate cancer and treatment with ADT had increased risk of incident fractures. The results were significant for any fracture, MOF and hip fracture in multivariate models compared to those with prostate cancer without ADT and compared to those without prostate cancer.

During the past decade, several epidemiological studies have presented relationships between ADT and an increased risk of incident fractures. One large study of more than 50,000 men with prostate cancer showed that within 5 years, 19.4% of those with ADT sustained a fracture, compared to 12.6% of those without ADT [14]. Another study of 3779 men with prostate cancer who received treatment with a GnRH agonist had a relative risk of 1.76 for hip fracture compared to a control group of 8341 with prostate cancer who were not treated with a GnRH agonist [15]. In a large matched cohort study of almost 20,000 men with prostate cancer and ADT, matched with "non-users", the HR for hip fracture was 1.65 for fragility fracture in the group with ADT [16].

In comparison to these previous studies, our results originate from a very large cohort of older men with and without prostate cancer with a large number of incident fractures. All patients in the cohort, including those without prostate cancer, were patients with high risk of osteoporotic fractures with a mean age of approximately 80 years and a large proportion had already suffered from a previous fracture. Thus, according to our results, the patients with prostate cancer and ADT truly represent an easily detected group with a very high risk of osteoporotic fractures. Furthermore, we have been able to adjust statistically not only for medical treatments such as any prescriptions of alendronate and calcium and vitamin D-supplements but also for established risk factors such as BMI, previous fractures, glucocorticoid treatment and rheumatoid arthritis, which resemble parameters in known risk calculators. Thus, the present study implicates that treatment with ADT increases the risk for fractures independently of many of the traditional risk factors

Table 5 Multivariate risk factor models within the separate groups

Multivariate risk factor model*	Patients without prostate cancer ($n = 159,662$)		Prostate cancer without ADT ($n = 13,128$)		Prostate cancer with ADT ($n = 6954$)	
Age (years)	1.05 (1.04–1.05)	$p < 0.001$	1.07 (1.06–1.08)	$p < 0.001$	1.04 (1.02–1.05)	$p < 0.001$
BMI (kg/m^2)	0.96 (0.95–0.96)	$p < 0.001$	0.97 (0.95–0.99)	$p = 0.001$	0.96 (0.94–0.98)	$p = 0.001$
Previous fracture	1.99 (1.90–2.07)	$p < 0.001$	2.53 (2.17–2.95)	$p < 0.001$	1.94 (1.63–2.31)	$p < 0.001$
Reumatoid arthritis	1.18 (1.02–1.37))	$p = 0.26$	1.63 (1.02–2.60)	$p = 0.042$	1.56 (0.84–2.90)	$p = 0.157$
Cortisone	1.09 (1.01–1.17)	$p = 0.19$	1.06 (0.83–1.36)	$p = 0.626$	0.92 (0.71–0.19)	$p = 0.534$
Secondary osteoporosis	1.31 (1.20–1.42)	$p < 0.001$	1.32 (0.94–1.84)	$p = 0.107$	1.20 (0.78–1.83)	$p = 0.412$
Estimated alcohol over consumption	1.67 (1.49–1. 86)	$p < 0.001$	1.28 (0.79–2.05)	$p = 0.315$	0.70 (0.29–1.70)	$p = 0.426$
Calcium + vitamin D	0.95 (0.88–1.04)	$p = 0.274$	1.07 (0.82–1.41)	$p = 0.619$	1.22 (0.93–1.61)	$p = 0.155$
Charlson morbidity index	1.00 (0.99–1.01)	$p = 780$	1.08 (1.04–1.10)	$p < 0.001$	1.04 (1.01–1.07)	$p = 0.009$
Previous fall	1.69 (1.62–1.76)	$p < 0.001$	1.75 (1.51–2.04)	$p < 0.001$	1.34 (1.12–1.60)	$p = 0.001$

*Age (years), BMI (kg/m2), previous fracture (*y*/*n*), rheumatoid arthritis (according to ICD), cortisone (any previous period the patient had retrieved prescriptions for more than 450 mg of prednisolone or equivalents over a period of 3 months or more, a dose corresponding to a daily treatment with at least 5 mg prednisolone for 3 months), secondary osteoporosis (secondary osteoporosis was defined as the presence of diagnoses of insulin dependent diabetes, hyperthyroidism, hypogonadism, malnutrition, osteogenesis imperfecta or chronic liver disease, estimated alcohol over consumption (over-consumption of alcohol was estimated according to several diagnoses of alcohol abuse together with alcohol related diseases according to ICD-codes) Charlson morbidity index, previous fall (*y*/*n*)

[27]. The final models were also adjusted for self-reported risk of falling (previous fall yes/no), which is a unique information in such a large cohort when studying risk for fractures.

We also detected an interaction between the different patient groups, the risk of fracture and age where for example a fictive 70-year-old patient with prostate cancer and ADT had an almost fourfold risk of hip fracture compared to a 70-year-old patient without ADT. Correspondently, we found that the 70-year-old patient with prostate cancer but without ADT had in fact a much lower risk for incident fractures compared to patient without prostate cancer, thus representing a low-risk subgroup compared to the general population. We believe that the interaction with age mirrors the increased fracture risk among the elderly in general (for multifactorial reasons) which contributes to smaller differences among the oldest old in statistical analyses. However, it is very important for urologist to comprehend that these two 70-year-old prostate cancer patients are to be regarded as completely different regarding fracture risk and those with ADT must be mandatorily evaluated regarding osteoporosis and antiresorptive medications.

Since the diagnosis of osteoporosis is very rarely used in the Swedish patient register (and extremely few patients are evaluated regarding osteoporosis in real life), we did not have reliable information regarding bone health in the dataset. Nevertheless, the relationship between treatment with ADT and osteoporosis has been known for almost 20 years and was recently presented in a meta-analysis of studies in prostate-cancer survivors [11]. In the same analysis, most of the ADT-patients were classified as either osteopaenic or osteoporotic (up to 85.0%), and the variation in the prevalence of osteoporosis in different studies (9.0–53.0%) was mainly influenced by ADT duration, disease stage, ethnicity and skeletal site used to diagnose osteoporosis. Furthermore, in one study, 618 men initiating ADT for prostate cancer were prospectively recruited and followed for 7 years. The prevalence of osteopenia and osteoporosis was very high already at treatment start in these patients (39% and 41%, respectively), leaving only 20% with normal bone density. A large proportion of the patients decreased their T-score by 1.0 and, after 3 years at least half of the patients who had a normal or osteopaenic BMD at treatment start had tripled their fracture risk [28]. Indeed, there is a rapid bone loss during the first 6–12 months of therapy [12] and this implicates the importance of detecting these patients at an early stage.

The Swedish population is characterised by one of the highest incidences of hip fracture in the world [29], and studies have shown that in Sweden, second to stroke, osteoporotic fractures account for more hospital-bed days yearly than any other diagnose [30]. In the present study, we found almost 11,000 fractures; and among these, almost 5000 were hip fractures. This is important since the hip fracture is indeed the most severe of the osteoporotic fractures and is associated with increased mortality in the general population [5]. An analysis based on the national Swedish Prostate Cancer Registry confirms that this is particularly true for men on ADT, with a two-times increase in deaths per 1000 person-years after hip fracture compared to the general male population [31].

Other known metabolic complications that are related to ADT are sexual dysfunction, gynecomastia, sarcopenia (reduced lean body mass) and body composition changes that may increase the risk of metabolic syndrome. This in turn impacts on fitness and the risk of falls may increase [11, 32]. However, in the present study, we did not see a significant relationship between treatment with ADT and the risk of

non-skeletal fall injury neither in the Cox regression models nor the Poisson models. This was indeed somewhat surprising as the relationship between ADT and the risk of fracture was strongly significant and implies that the effect of ADT on fracture incidence is primarily mediated through skeletal changes. To our knowledge, this is the first study in such a large cohort where non-skeletal fall injury could be investigated together with fractures. This strengthens the indications for bone-specific medical treatments of this group. However, in Sweden, a devastating small proportion of high-risk patients is normally considered for osteoporotic medications and only 3% of men, aged 50 or more with a previous fragility fracture are offered medical treatment [33]. In the present study, a very small proportion (only 4%) of the patients with ADT had ever been prescribed alendronate although almost a third had suffered from a previous fracture. One may speculate that by the time this cohort was collected (2008–2014), little attention was given to bone health in this patient group. Furthermore, given the fact that the patient with ADT generally suffers from other side-effects, as stated previously, very few patients (or physicians) may be concerned about the silent disorder of osteoporosis. However, during the past years, the research field of the efficacy of osteoporotic medications in this patient group has increased. A recently published meta-analysis presented that both oral and intravenous bisphosphonates and denosumab were effective in reducing the rate of bone loss when compared to placebo. Furthermore, patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5%, vs. 3.9% with placebo, RR = 0.38; $p = 0.006$) [34, 35]. In the present study, there were too few patients prescribed both alendronate and ADT in order to do any statistical calculations. However, we have recently presented another study from the same original cohort, where alendronate significantly reduced the risk of incident fractures (HR 0.66, $p < 0.01$) and even reduced mortality in men and women (80 years or older) with a previous fracture [20].

There are limitations with this study. We did not have access to measurements of BMD, smoking or alcohol use in the databases and vertebral fractures that are often bypassed and not diagnosed in registers could not be reliably studied in this cohort. On the other hand, we estimate that largely all hip fractures were detected since this diagnosis is established at emergency units and hospital wards, all connected to the national registers. Furthermore, we did not have any detailed clinical information regarding their prostate cancer such as Gleason score. One strength of this study is that we have indeed BMI and self-reported information on previous falls which are unique features of such a large database and of great importance in studies of fracture risk.

In conclusion, our results confirm that patients with prostate cancer and ADT have increased risk of incident osteoporotic fractures. This was significant also after multivariate adjustment for traditional fracture-related risk factors, and the differences in risk were most prominent in younger patients where the treatment with ADT contributed to an almost four-fold risk of incident hip fracture compared to those with prostate cancer but without ADT. We also found that there were no clinically relevant relationships between treatment with ADT and incident non-skeletal fall injury which further strengthens the assumption that the relationship between ADT and fracture is primarily bone-related. Although all patients with prostate cancer and ADT should be considered as "high risk patients", we found that within this group, the only clinically relevant risk factors for incident fracture were high age, low BMI, previous fracture and/or previous falls and other traditional risk factors did not contribute significantly in the statistical models. We believe that further effort in acknowledging this fragile patient group must be taken and that osteoporosis medications should be considered as routine procedures in all patients with prostate cancer already at the initiation of androgen deprivation therapy.

Compliance with ethical standards

Conflicts of interest Märit Wallander has has received lecture fees from Amgen and Meda, and consulting fees from Amgen and UCB Pharma. Kristian F Axelsson has received lecture fees from Meda/Mylan, Lilly and Amgen.

Dan Lundh has no conflicts of interest. Mattias Lorentzon has received lecture fees from Amgen, Lilly, Meda, Renapharma, UCB Pharma, and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma and Consilient Health.

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