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The implications of baseline bone-health assessment at initiation of androgen-deprivation therapy for prostate cancer

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Objectives

To assess bone-density testing (BDT) use amongst prostate cancer survivors receiving androgen-deprivation therapy (ADT), and downstream implications for osteoporosis and fracture diagnoses, as well as pharmacological osteoporosis treatment in a national integrated delivery system.

Patients and methods

We identified 17 017 men with prostate cancer who received any ADT between 2005 and 2014 using the Veterans Health Administration cancer registry and administrative data. We identified claims for BDT within a 3-year period of ADT initiation. We then used multivariable regression to examine the association between BDT use and incident osteoporosis, fracture, and use of pharmacological treatment.

Results

We found that a minority of patients received BDT (n = 2 502, 15%); however, the rate of testing increased to >20% by the end of the study period. Men receiving BDT were older at diagnosis and had higher-risk prostate cancer (both $P <$ 0.001). Osteoporosis and fracture diagnoses, use of vitamin D ± calcium, and bisphosphonates were all more common in men who received BDT. After adjustment, BDT, and to a lesser degree ≥2 years of ADT, were both independently associated with incident osteoporosis, fracture, and osteoporosis treatment.

Conclusions

BDT is rare amongst patients with prostate cancer treated with ADT in this integrated delivery system. However, BDT was associated with substantially increased treatment of osteoporosis indicating an underappreciated burden of osteoporosis amongst prostate cancer survivors initiating ADT. Optimising BDT use and osteoporosis management in this at-risk population appears warranted.

Keywords

prostatic neoplasms, bone density, osteoporosis, fractures, bone, anti-androgen effect, #PCSM, #ProstateCancer

Introduction

Prostate cancer is a common malignancy in American men, many of whom eventually undergo androgen-deprivation therapy (ADT) as part of their prostate cancer management [1,2]. Whilst ADT may be warranted to treat high-risk and advanced disease, it is associated with significant, often under-appreciated, adverse effects related to hypogonadism, including metabolic syndrome, cardiovascular disease, and decreased bone health [3].

The effects of ADT on bone manifest as significantly decreased bone-mineral density (BMD), and consequently increased fracture risk [4–8]. Guidelines and existing literature recommend screening for osteoporosis at the time of ADT initiation to facilitate risk stratification and early

pharmacological intervention where appropriate [9–13]. The National Comprehensive Cancer Network (NCCN) Task Force Report: Bone Health in Cancer Care states that 'in patients who will be undergoing therapy that lowers sex steroids, the NCCN Guidelines for Breast and Prostate Cancers recommend evaluation with baseline and periodic follow-up DXA scans to evaluate bone health and risk of fracture' [14]. However, existing data show that bone-density testing (BDT) rates remain below optimal levels [15–20]. Bone-health assessment is especially warranted in patients with other risk factors for skeletal-related events, e.g. smoking, alcohol use, and low vitamin D levels [21]. These risk factors disproportionately afflict American veterans, who subsequently have higher rates of mortality after fractures, further magnifying the need for BDT [22]. Despite these increased risks, the national patterns of BDT use and subsequent osteoporosis management in this population have not been well categorised.

In this context, we characterised BDT use and outcomes in a national integrated delivery system cohort of veteran patients with prostate cancer treated with ADT. We evaluated BDT rates at the initiation of ADT, and assessed downstream skeletal-related outcomes including osteoporosis, fracture, and pharmacological treatment for osteoporosis. Better understanding of bone-health practice patterns and outcomes through this study will help to define the burden of bone disease amongst patients with high-risk prostate cancer and opportunities to improve the quality of their care.

Patients and Methods

Study Population

We used the Veterans Administration (VA) Central Cancer Registry to identify patients with an incident diagnosis of pathologically confirmed prostate cancer between 2005 and 2008 who were treated with ADT, defined as surgical orchidectomy or medical castration with an injectable GnRH agonist, using inpatient and outpatient pharmacy and utilisation coding [16]. More than 99% of the men in this cohort received medical castration, amongst whom 93% received goserelin, 4% leuprolide, and 3% another agent. We excluded patients with other cancer diagnoses, death within 30 days of diagnosis, or diagnosis at autopsy. We linked these data with VA administrative files containing inpatient, outpatient, laboratory, radiology, pharmacy, and facility data with follow-up through the year 2014. This allowed us to examine ADT use as well as BDT and other skeletal-related outcomes. We identified a cohort of 17 017 patients.

Outcomes

Our primary outcome was receipt of BDT at the patient level, consisting of either dual X-ray absorptiometry or quantitative CT. We assessed BDT by identifying claims submitted within 18 months before or after initiation of ADT, which should capture both recommended testing before ADT initiation as well as any delayed or follow-up monitoring. We utilised a larger time window than previous studies in order to maximise our capture of BDT performed surrounding ADT. As such our BDT rates may be biased to be slightly higher than those of other studies on this topic. Our secondary outcomes were downstream bone-health measures, including any administrative codes suggesting a new diagnosis of osteoporosis or any fracture after ADT initiation. We also queried pharmacy claims for any new prescriptions suggesting osteoporosis treatment after induction of ADT. Specifically, we assessed for dispensing of vitamin D ± calcium (calcium carbonate, calcium citrate, calcium acetate, calcium) as recommended for all patients initiating ADT, bisphosphonates (alendronate, pamidronate, risedronate, zoledronic acid, ibandronate), or denosumab, a bone-health treatment for metastatic prostate cancer that has also been shown to increase BMD and lower fracture rates in men receiving ADT [23].

Statistical Analysis

We used descriptive statistics to assess differences in demographics, disease, and treatment characteristics between patients with prostate cancer treated with ADT who received BDT and those who did not. We examined covariates including age, race, ethnicity, marital status, employment status, Gleason score, D'Amico prostate cancer risk group, primary prostate cancer treatment, and Charlson Comorbidity Index (CCI) score (calculated using healthcare claims for the 12 months prior to prostate cancer diagnosis) [24,25]. We used Student's *t*-tests and chi-squared testing as appropriate.

To assess the independent association of BDT use with our secondary outcomes of incident osteoporosis, fracture, and osteoporosis treatment, we fitted separate multiple logistic regression models for each outcome with the primary exposure of BDT. Given its particularly detrimental impact on bone health, we adjusted these models using an indicator variable for ≥2 years of ADT [4–8], as well as the following covariates: age, race, ethnicity, marital status, D'Amico risk score, prostate cancer treatment type, and CCI score.

All analyses were conducted using Statistical Analysis System (SAS) software (SAS Institute, Cary, North Carolina, USA) and all testing was two-sided using an α of 0.05. This study was approved by the VA Ann Arbor Healthcare System Institutional Review Board.

Results

Amongst the 17 017 patients with prostate cancer receiving ADT, a minority received BDT during the study period (2

502, 15%). As shown in Table 1, men receiving BDT were older and diagnosed with higher-risk disease ($P < 0.001$ for both). Amongst patients who received BDT there were slightly lower rates of initial treatment with a combination of radiation therapy and ADT ($P < 0.001$). Testing rates increased consistently over the years of the study period, as shown in Fig. 1.

Bone-health outcomes amongst men with prostate cancer treated with ADT who did and did not receive BDT are shown in Table 2. Recipients of BDT were significantly more likely to be diagnosed with osteoporosis and fracture, and more likely to receive treatment for osteoporosis ($P < 0.001$ for all). As shown in Fig. 2, differences in bone-health outcomes amongst patients after the receipt of BDT were dramatic. For example, after BDT, diagnoses of osteoporosis and fracture increased nearly 10- and three-fold respectively. In addition, rates of vitamin D use more than doubled after BDT, while bisphosphonate use also increased ~10-fold. Denosumab was rare but its use also increased.

As shown in Table 3, after adjustment for patient and disease characteristics, BDT remained associated with the diagnosis (adjusted odds ratio [aOR] 6.21, 95% CI: 5.40–7.15) and treatment of osteoporosis (aOR 6.47, 95% CI: 5.66–7.39), as well as slightly increased odds of fracture diagnosis (aOR 1.29, 95% CI: 1.08–1.53). Similarly, although to a lesser degree, the receipt of ≥2 years of ADT was significantly associated with diagnosis (aOR 1.47, 95% CI: 1.28–1.69) and treatment of osteoporosis (aOR 1.86, 95% CI: 1.71–2.03), in addition to incident fracture diagnosis (aOR 1.21, 95% CI: 1.06–1.40).

Table 1 Characteristics of patients on ADT according to BDT.

Characteristic	No BDT	BDT	P
Number of patients	14 515	2 502	
Age at diagnosis, mean (SD)	68.6 (9.1)	70.1 (9.3)	<0.001
Race, %			
White	67	66	0.05
Black	29	31	
Other/Unknown	4	3	
Ethnicity, %			
Hispanic	5	10	<0.001
Non-Hispanic	94	89	
Unknown	1	1	
Marital status, %			
Married	49	49	0.30
Divorced/separated	29	27	
Single/never married	8	9	
Widowed	13	15	
Unknown	<1	<1	
Status, %			
Alive	74	72	0.07
Dead	26	28	
Employment status, %			
Full-time	7	6	0.50
Part time	3	3	
Retired	53	54	
Self-employed	2	2	
Unemployed	34	34	
Active military	<1	<1	
Unknown	1	<1	
Gleason score, %			
6	25	21	<0.001
7	42	38	
8–10	33	41	
Risk group, %			
Low	14	11	<0.001
Intermediate	32	27	
High	54	63	
Initial treatment, %			
Observation	6	6	<0.001
ADT monotherapy	36	38	
Surgery	8	10	
Radiation	5	6	
Surgery + radiation	1	<1	
Radiation + ADT	35	28	
Other	<1	1	
Unknown	8	9	
CCI score, %			
0	42	40	0.22
1	27	27	
≥2	31	33	
≥2 years ADT, %	32	38	<0.001

Fig. 1 Rate of BDT across the years of the study period, with the number of men initiating ADT each year represented by the size of the circle. Year 2014 is not shown as there were <50 patients initiating ADT.

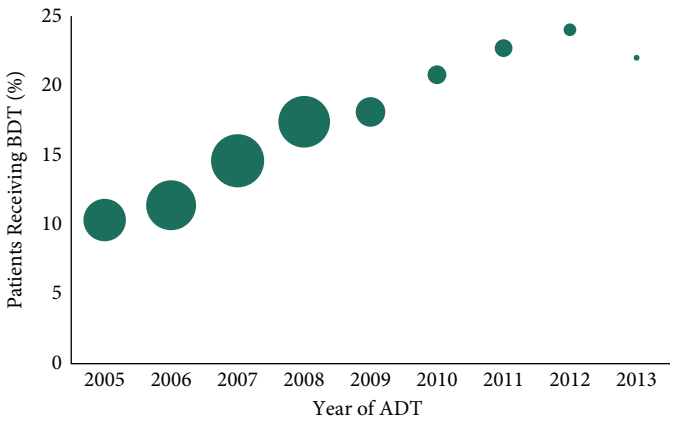
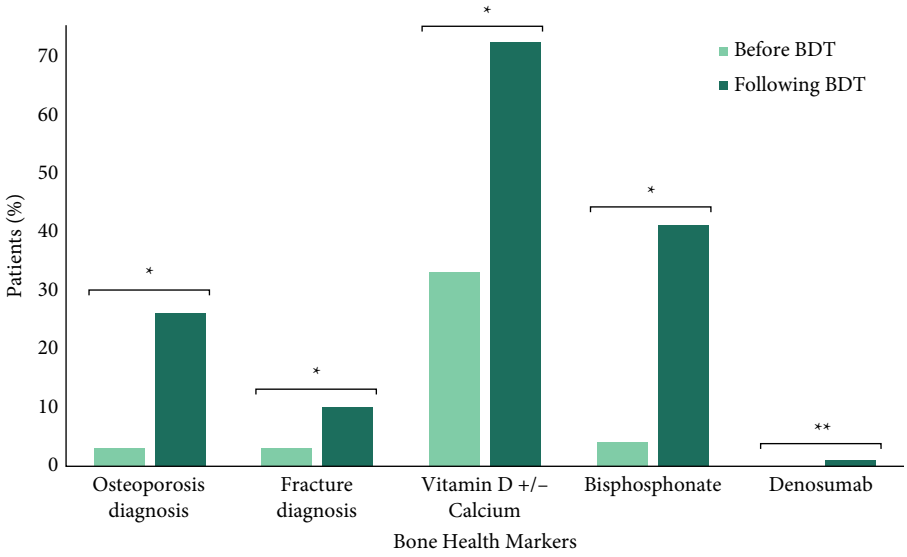


Table 2 Osteoporosis, fracture, and pharmacological osteoporosis treatment amongst prostate cancer survivors on ADT according to BDT.

Characteristic	No BDT, n (%)	BDT, n (%)	P
Number of patients	14 515 (100)	2 502 (100)	
Osteoporosis diagnosis	752 (5)	669 (27)	<0.001
Fracture diagnosis	1 132 (8)	270 (11)	<0.001
Osteoporosis treatment			
Vitamin D* ± calcium†	5 067 (35)	1 848 (74)	<0.001
Bisphosphonate‡	1 983 (14)	1 033 (41)	<0.001
Denosumab	31 (0.2)	14 (0.6)	<0.001

Vitamin D, ergocalciferol, cholecalciferol, 1,25 dihydroxycholecalciferol; †Calcium carbonate, calcium citrate, calcium acetate, calcium; ‡Alendronate, pamidronate, risedronate, zoledronic acid, ibandronate.

Fig. 2 Comparison of bone health-related diagnoses and treatments amongst men with prostate cancer receiving ADT before and after undergoing BDT. Amongst patients with prostate cancer initiating ADT, BDT was associated with dramatic increases in the diagnosis of osteoporosis and fracture. In addition, bisphosphonate use increased ~10-fold, whilst vitamin D use more than doubled after BDT.



* $P<0.001$

** P value not obtainable as no patients were taking denosumab prior to receiving BDT

Table 3 Multivariable regression results for BDT and ≥2 years of ADT after adjustment for patient and disease characteristics.

Outcome	BDT aOR (95% CI)*	≥2 years ADT aOR (95% CI)*
Osteoporosis diagnosis	6.21 (5.40–7.15)	1.47 (1.28–1.69)
Osteoporosis treatment	6.47 (5.66–7.39)	1.86 (1.71–2.03)
Fracture diagnosis	1.29 (1.08–1.53)	1.21 (1.06–1.40)

**Adjusted for age, race, ethnicity, marital status, D'Amico risk score, prostate cancer treatment type, and CCI score.*

Discussion

We found that roughly one in seven patients with prostate cancer receiving ADT underwent BDT within the 3 years surrounding initiation of castration in this national integrated delivery system. However, by the end of the study period in 2014 this number had increased to more than one in five. BDT was associated with dramatic increases in the diagnosis and treatment of osteoporosis, suggesting a non-trivial underlying burden of bone disease in untested men. Whilst good clinical judgment regarding which patients would benefit most from testing may lead to selection bias, it is unlikely that the nearly 90% of untested men in our cohort were at uniformly low-risk of osteoporosis and fracture. Even after controlling for patient and disease characteristics, both BDT and, to a lesser degree, an extended duration of ADT, were independent predictors of osteoporosis and fracture diagnoses. These findings confirm efforts are necessary to encourage bone-health testing and osteoporosis treatment in this high-risk population of prostate cancer survivors to decrease avoidable harms of castration with ADT.

Our present findings are consistent with prior data showing low rates of BDT in patients receiving ADT. Within veterans specifically, our present finding of a 15% BDT rate is congruent with previously published rates of ~13% a decade ago, indicating a persistent quality gap [19,20]. Although the uptrend in testing rates observed in the present study is encouraging, 20% of patients undergoing BDT is still well below an ideal testing rate. Whilst prior studies in veterans were limited to smaller geographical areas capturing several hundred patients, our national cohort is much larger, representing veterans across the USA, and reflects more contemporary practice patterns. Indeed, data from large studies in Medicare populations have also found persistently low rates varying from 6% to 14.5%, albeit with trends towards increasing utilisation over time, signalling systematic poor compliance with recommended care [16–18]. Recent results from other clinical contexts also underscore that the problem of low rates of BDT use among patients at high risk for bone-related complications extends beyond the realm of prostate cancer into breast cancer [26].

The osteoporosis and fracture diagnoses identified in the present study underscore the importance of appropriate bone-health testing amongst high-risk prostate cancer survivors. The striking five-fold difference in osteoporosis diagnosis between those who did and did not receive BDT suggests a significant amount of underlying disease in the 85% of men who were not tested. Moreover, the 10-fold increase in osteoporosis diagnosis after BDT, and two- to three-fold higher rates of osteoporosis treatment in the tested group compared to untested men demonstrates that testing yields actionable information for clinicians, who can intervene to potentially help avoid downstream bone complications especially in light of initiating ADT. Although the increases in fracture diagnoses were more modest, presumably discovered incidentally during evaluation for osteoporosis, this is a morbid complication highlighting that improvements in identification and treatment of skeletal fractures may be warranted.

In combination with the existing literature, our present findings support efforts to increase rates of appropriate BDT in men undergoing ADT, and suggest that such testing could in turn yield improved diagnosis and treatment of ADT's adverse effects on the skeletal system. However, exploring the behaviours and norms of physicians and patients that contribute to persistently poor compliance with guideline-recommended bone-health assessment amongst men on ADT is critical and should help inform subsequent intervention design. At least four addressable reasons may be driving our present observations. First, providers may be unaware of the guideline recommendations to screen men receiving ADT for osteoporosis issued by groups such as the NCCN, although the negative impacts of ADT on bone health have long been established [14,27]. Second, many clinicians may not feel comfortable using instruments such as the fracture risk assessment model (FRAX) tool, which combines BDT results with clinical risk factors to guide treatment (although it can be calculated without BMD) [28]. Third, there may be fragmentation amongst providers caring for these patients. Whilst specialists order and manage ADT, in the absence of metastatic disease it is often primary care clinicians who are tasked with the diagnosis and treatment of osteoporosis in men with prostate cancer. Last, the evidence supporting the impact of vitamin D, calcium, and bisphosphonates on decreasing clinically relevant fractures is mixed, generating confusion about the efficacy of these interventions and decreasing the likelihood of their utilisation [29,30]. However, current recommended care includes placing men aged >50 years on vitamin D and calcium supplementation, a target not achieved in most of the present cohort [31]. It is possible some men in the present study may have obtained these supplements over the counter, but this is unlikely given VA pharmacy coverage and cost differences. Future work must better clarify the impacts of BDT and pharmacological intervention on subsequent fracture rates. Taken together, these findings suggest that further study is needed to address this gap in high-risk prostate cancer care and men's health in general.

There are several limitations to the present study. First, our results may not be generalisable to all patients with prostate cancer treated with ADT, as additional risks and unmeasured differences may be present amongst veterans. However, our present findings are consistent with results from other non-VA datasets, and the issues of low rates of BDT and low rates of subsequent treatment are not unique to this population. Further, our nationally representative cohort and the lack of age exclusions, as in Medicare studies, increases generalisability. Second, although our present study includes patients with follow-up through 2014, the 9-year span of our cohort from incident cancer diagnosis to last follow-up may suggest that our observed BDT rate could be an underestimate of current rates. However, the consistency of findings across studies and negligible increases indicate a persistent gap in care. Third, these retrospective data do not include the actual indications for BDT (other than initiating ADT) and therapeutic interventions, only whether or not they were received. Nonetheless, our use of incident diagnosis and pharmacy codes, coupled with our study design, support our conclusions of significantly underappreciated bone disease burden amongst these patients regardless of testing indication. It is possible that our present analysis may be an underestimate of the rates at which physicians are assessing osteoporotic fracture risk in these men, as we do not capture assessment methods that do not include BMD. However, given that BDT is the 'gold standard' method and is the approach recommended by the NCCN, we believe that these methods likely capture most of the bone-health assessments being performed in this population. It is also important to note that BDT is not causally associated with osteoporosis or fracture. Rather, the use of BDT allows for the identification of potentially subclinical bone disease, which can subsequently lead to earlier intervention and long-term reduction of harm. Lastly, our present analysis is subject to the inherent limitations of observational research and whilst we have attempted to control for confounding with multiple regression techniques, we were not able to fully account for unobserved confounders.

These limitations notwithstanding, our present results have important implications for men receiving ADT and those involved their care. First, urologists must be vigilant to minimise the burdens related to the adverse effects of ADT on bone health. Despite evidence recommending BDT in patients on ADT and trends towards increased use, rates of appropriate testing remain well below optimal levels. Second, from the standpoint of payers and policymakers, the costs of ADT-related adverse effects are significant, and interventions focused on mitigating the skeletal impacts of ADT have been

found to be cost-effective [32]. Increased attention should be directed towards encouraging the use of BDT in these patients. Last, the effects of ADT, osteoporosis, and fractures have significant negative implications for quality of life and survival. Increased use of appropriate BDT can potentially facilitate improved patient wellbeing and outcomes.

There appears to be significant under-diagnosis and treatment of osteoporosis amongst men with prostate cancer receiving ADT. Our present findings suggest substantial opportunities exist to reduce bone-related complications by improving use of BDT at ADT initiation to allow for early intervention. Better understanding of how providers care for these patients who are at high risk for bone-related complications, and how to most effectively target interventions to increase bone-health assessment is justified. In addition, quantifying the degree to which improved detection and treatment of osteoporosis can help in lower clinically relevant fracture rates in this high-risk population may help foster guideline concordant care. Efforts to optimise BDT amongst prostate cancer survivors initiating ADT may lead to increased quality of life and care.

Conflicts of Interest

None. The contents do not represent the views of the USA Department of Veterans Affairs or the USA Government.

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References

1 **National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program**. *Cancer Stat Facts: Prostate Cancer*. Available at: https://seer.cancer.gov/statfacts/html/prost.html. Accessed January 2017.

2 **Shahani S, Braga-Basaria M, Basaria S**. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. *J Clin Endocrinol Metab* 2008; 93: 2042–9

3 **Ostergren PB, Kistorp C, Bennedbaek FN, Faber J, Sonksen J, Fode M**. The use of exercise interventions to overcome adverse effects of androgen deprivation therapy. *Nat Rev Urol* 2016; 13: 353–64

4 **Wei JT, Gross M, Jaffe CA et al.** Androgen deprivation therapy for prostate cancer results in significant loss of bone density. *Urology* 1999; 54: 607–11

5 **Shahinian VB, Kuo YF, Freeman JL, Goodwin JS**. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005; 352: 154–64

6 **Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM**. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab* 2005; 90: 6410–7

7 **Morgans AK, Fan KH, Koyama T et al.** Bone complications among prostate cancer survivors: long-term follow-up from the prostate cancer outcomes study. *Prostate Cancer Prostatic Dis* 2014; 17: 338–42

8 **Shao YH, Moore DF, Shih W, Lin Y, Jang TL, Lu-Yao GL**. Fracture after androgen deprivation therapy among men with a high baseline risk of skeletal complications. *BJU Int* 2013; 111: 745–52

9 **Bae DC, Stein BS**. The diagnosis and treatment of osteoporosis in men on androgen deprivation therapy for advanced carcinoma of the prostate. *J Urol* 2004; 172: 2137–44

10 **Bienz M, Saad F**. Androgen-deprivation therapy and bone loss in prostate cancer patients: a clinical review. *Bonekey Rep* 2015; 4: 716

11 **Saad F, Adachi JD, Brown JP et al.** Cancer treatment-induced bone loss in breast and prostate cancer. *J Clin Oncol* 2008; 26: 5465–76

12 **Skolarus TA, Caram MV, Shahinian VB**. Androgen-deprivation-associated bone disease. *Curr Opin Urol* 2014;24:601–7.

13 **Zhumkhawala AA, Gleason JM, Cheetham TC et al.** Osteoporosis management program decreases incidence of hip fracture in patients with prostate cancer receiving androgen deprivation therapy. *Urology* 2013; 81: 1010–5

14 **Gralow JR, Biermann JS, Farooki A et al.** NCCN Task Force Report: Bone Health in Cancer Care. *J Natl Compr Canc Netw* 2009;7(Suppl. 3): S1–32; quiz S33-35.

15 **Tanvetyanon T**. Physician practices of bone density testing and drug prescribing to prevent or treat osteoporosis during androgen deprivation therapy. *Cancer* 2005; 103: 237–41

16 **Shahinian VB, Kuo YF**. Patterns of bone mineral density testing in men receiving androgen deprivation for prostate cancer. *J Gen Intern Med* 2013; 28: 1440–6

17 **Morgans AK, Smith MR, O'Malley AJ, Keating NL**. Bone density testing among prostate cancer survivors treated with androgen-deprivation therapy. *Cancer* 2013; 119: 863–70

18 **Suarez-Almazor ME, Peddi P, Luo R, Nguyen HT, Elting LS**. Low rates of bone mineral density measurement in Medicare beneficiaries with prostate cancer initiating androgen deprivation therapy. *Supp Care Cancer* 2014; 22: 537–44

19 **Wilcox A, Carnes ML, Moon TD et al.** Androgen deprivation in veterans with prostate cancer: implications for skeletal health. *Ann Pharmacother* 2006; 40: 2107–14

20 **Yee EF, White RE, Murata GH, Handanos C, Hoffman RM**. Osteoporosis management in prostate cancer patients treated with androgen deprivation therapy. *J Gen Intern Med* 2007; 22: 1305–10

21 **Chang P, Regan MM, Ferrer M et al.** Relief of urinary symptom burden after primary prostate cancer treatment. *J Urol* 2017; 197: 376–84

22 **Bass E, Campbell RR, Werner DC, Nelson A, Bulat T**. Inpatient mortality of hip fracture patients in the Veterans Health Administration. *Rehabil Nurs* 2004; 29: 215–20

23 **Smith MR, Egerdie B, Hernandez Toriz N et al.** Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009; 361: 745–55

24 **Charlson ME, Pompei P, Ales KL, MacKenzie CR**. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–83

25 **Quan H, Sundararajan V, Halfon P et al.** Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43: 1130–9

26 **Stratton J, Hu X, Soulos PR et al.** Bone density screening in postmenopausal women with early-stage breast cancer treated with aromatase inhibitors. *J Oncol Pract* 2017; 13: e505–15

27 **Theriault RL, Biermann JS, Brown E et al.** NCCN Task Force Report: Bone Health and Cancer Care. *J Natl Compr Canc Netw* 2006;4(Suppl. 2): S1–20; quiz S21-22.

28 **Saylor PJ, Smith MR**. Bone health and prostate cancer. *Prostate Cancer Prostatic Dis* 2010; 13: 20–7

29 **Moyer VA, U.S. Preventive Services Task Force**. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013; 158: 691–6

30 **Saylor PJ**. Bone targeted therapies for the prevention of skeletal morbidity in men with prostate cancer. *Asian J Androl* 2014; 16: 341–7

31 **National Comprehensive Cancer Network**. *NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer* v2.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed June 2017.

32 **Ito K**, **Elkin EB**, **Girotra M**, **Morris MJ**. Cost-effectiveness of fracture prevention in men who receive androgen deprivation therapy for localized prostate cancer. *Ann Intern Med* 2010; 152: 621–9

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Abbreviations: ADT, androgen-deprivation therapy; aOR, adjusted odds ratio; BDT, bone-density testing; BMD, bone-mineral density; CCI, Charlson Comorbidity Index; NCCN, National Comprehensive Cancer Network; VA, Veterans Administration.

