Bone complications among prostate cancer survivors: long-term follow-up from the prostate cancer outcomes study

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INTRODUCTION
Prostate cancer is the most common non-cutaneous malignancy in men in the United States.¹ Androgen deprivation therapy (ADT), through orchiectomy or the use of gonadotropin-releasing hormone agonists or antagonists, is the most frequently used systemic therapy for prostate cancer. At present, over 600,000 prostate cancer survivors with various states of the disease are receiving ADT in the United States.² Although widely used and considered safe by oncology standards, ADT is not without complications. Recognizing the risks from and managing the complications of ADT exposure have become critical components of survivorship care for men with prostate cancer.

Bone-related complications of ADT include loss of bone mineral density (BMD) and an increased risk of fractures.³ The consequences of hip fractures for survivors of prostate cancer are especially grave, given that the risk of death at 1 year after hip fracture is 31–35% for men, as compared with 17–22% for women.⁴ Bone-related complications of ADT have been reported in retrospective studies of large administrative databases, as well as smaller prospective studies.³⁵–⁹ However, these studies are limited by relatively short follow-up, and, when based on Surveillance, Epidemiology and End Results (SEER) Medicare linked data, only include men over the age of 65 years at diagnosis. Assessing men exposed to ADT across an array of age groups is crucial as the risk of ADT-associated fragility fracture is associated with duration of exposure to ADT in men of any age.³ Additionally, national guideline recommendations regarding BMD testing and bone-targeted medications are not age dependent. The Prostate Cancer Outcomes Study (PCOS) is a population-based cohort of men diagnosed with prostate cancer in 1994–1995, identified by one of six SEER tumor registries, and followed for up to 15 years after diagnosis. As such, the PCOS may allow us to overcome some of the limitations of prior studies and provide a more generalizable portrait of the long-term complications of ADT in men with prostate cancer.

The aim of our study was to investigate long-term bone complications associated with ADT in a population-based cohort of prostate cancer survivors followed for up to 15 years after diagnosis. We assessed patient-reported bone health outcome measures, including the development of fracture, the frequency of BMD testing and the use of bone-targeted medications for osteoporosis treatment or fracture prevention. We hypothesized that men treated with prolonged ADT would report fracture, BMD testing and bone-targeted medication use more commonly than untreated men, and that short-term ADT exposure would not be associated with these outcomes.

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MATERIALS AND METHODS

Study design

The PCOS enrolled incident prostate cancer patients aged 39–89 years from six participating SEER sites (Connecticut, Utah, New Mexico, and the metropolitan areas of Atlanta, GA, Los Angeles, CA, and Seattle-Puget Sound, WA) between 1 October 1994 and 31 October 1995, randomly sampling 5672 subjects from 11 137 eligible prostate cancer cases. A rapid case ascertainment system was used to identify patients as close to diagnosis as possible. A prespecified sampling strategy was used that oversampled younger men, Hispanics and African Americans (to ensure a representative population of United States prostate cancer patients), while maintaining adequate sample size to address key research questions.10,11 Institutional Review Boards at all participating sites approved the study.

Eligible men were asked to complete a self-administered baseline survey within approximately 6 months after diagnosis. This survey included items on clinical and sociodemographic factors, comorbid conditions (modified from the Charlson Comorbidity Index), health-related quality of life, age at diagnosis, race/ethnicity, marital status, income level, education level and insurance type.12,13 Information regarding treatment for prostate cancer (surgery, radiation, hormonal therapy, no therapy or any combination of therapies) and tumor characteristics (Gleason score, highest diagnostic PSA level, disease stage) was collected from a detailed 1-year medical record review as described previously and was coded according to SEER guidelines.10–14 Participants were contacted again at 1, 2, 5 and 15 years following diagnosis and asked to complete a survey containing items on further prostate cancer treatment, including past or current use of ADT, incident comorbid conditions, clinical outcomes and health-related quality of life. The long-term (15 years after diagnosis) survey included specific items on bone health.

Study population

To be included in this analysis, PCOS participants must have had non-metastatic disease at the time of diagnosis and completed a long-term (15 years) patient survey. Specific questions in the survey assessed whether men had developed bone metastases or fracture, as well as receipt of a BMD test or bone medications. Of the initial 3533 PCOS participants who completed a baseline survey, 1782 were alive at the time of 15-year follow-up. Of these, 998 (56%) completed the 15-year survey. Thirty-seven of these men had metastatic disease at diagnosis and were excluded from our analysis, resulting in an analytic cohort of 961 men. Twelve men with metastatic disease at the time of the long-term survey were excluded from the fracture analysis as we were unable to distinguish between pathologic fractures due to metastatic disease and fragility fractures due to low BMD. Patient non-response resulted in missing data for fracture (7), BMD test (107) and bone medications (34). Missing data was counted as not reporting fracture, receipt of a BMD test or bone medication use.

Statistical analysis

Independent variables. We categorized participants into the following exposure subgroups based on 1-year medical record review data and self-report of receipt of ADT at 6 months, 1, 2, 5 and 15 years after diagnosis: no ADT, short-term ADT (total ADT duration of 1 year or less) and prolonged ADT (total ADT duration of more than 1 year). Short-term ADT was defined as ≤1 year of ADT exposure because this duration has been used in previous studies to define ADT duration, and was more reliably defined from our survey data than other commonly used durations like 4–6 months.15–17 ADT exposure was defined in the survey question as treatment with gonadotropin-releasing hormone agonist therapy, anti-androgen medications or a combination of these. We included the following covariates in our models: age at diagnosis, race, Charlson comorbidity score, marital status and Gleason score. All covariates included in the multivariable analysis were chosen based on perceived clinical relevance before univariable analysis.

Dependent variables

Fracture, BMD testing and bone medication use: Patients were specifically queried regarding the development of fracture, and the use of BMD testing or bone-targeted medications, including calcium, vitamin D, zoledronic acid, alendronate, risedronate, calcitonin and parathyroid hormone, in the long-term survey. Statistical methods: We computed descriptive statistics to compare distributions of patient baseline characteristics and outcome variables across ADT exposure groups. We assessed the relationship between reported duration of ADT exposure and reported development of fracture, receipt of BMD testing or bone medication use using univariable logistic regression. We then assessed the association between ADT exposure and fracture, receipt of BMD testing and bone medication use using weighted multivariable logistic regression adjusted for ADT exposure, age at diagnosis, race, marital status, Gleason score and Charlson comorbidity score. All tests of statistical significance were two sided, and P-values < 0.05 were considered statistically significant. We used R statistical software version 2.15.1 and the associated survey package for our analyses.18–20

RESULTS

Study population

Baseline characteristics of the 961 men diagnosed with non-metastatic prostate cancer who provided patient-reported outcomes 15 years following diagnosis are included in Table 1. In this population, 684 did not report ADT use, 120 men reported ≤1 year of ADT and 157 reported >1 year of ADT exposure (Table 1). Rates of survey completion were similar among ADT exposure groups, with 86% of no ADT and 85% of the short-term and prolonged ADT groups returning surveys at all time points. There were small but significant differences between participants in different treatment groups in terms of age at diagnosis, race and education level. A greater percentage of men reporting ADT use had high-grade disease (Gleason scores of 8–10), were treated with radiation rather than prostatectomy and had slightly higher comorbidity scores than men not reporting ADT.

Study outcome

The risk of self-reported fracture was 10% in the entire cohort, 9.5% in untreated men, 9% in men reporting treatment with short-term ADT (≤1 year) and 15% among men reporting treatment with prolonged ADT (>1 year) (P = 0.18). The overall reported frequency of BMD testing in the cohort was 27%, with 28% of men reporting short-term ADT exposure, and 49% of men reporting prolonged ADT exposure (P < 0.001). On univariable analysis, men reporting short-term ADT exposure (≤1 year) did not have an increased probability of reporting fracture, BMD testing or bone medication use compared with men not reporting treatment with ADT (Table 2). Men reporting treatment with prolonged ADT had increased odds of reporting fracture, BMD testing and bone medication use compared with men not reporting treatment with ADT (Table 2).

Bone medication use varied by duration of exposure to ADT and medication type. Among men reporting prolonged ADT, 50.3% reported treatment with bone medications, compared with 24.7% and 31.7% of men not reporting treatment with ADT and men reporting short-term ADT treatment, respectively (P < 0.001). Of men reporting bone medication use, 94% reported calcium or vitamin D use and 6% reported bisphosphonate use (including intravenous and oral formulations) (P < 0.001). We used weighted logistic regression to assess the association between reported ADT treatment duration and reported development of fracture at 15 years accounting for patient-level covariates (Table 3). Men reporting short-term use of ADT did not have increased odds of fracture or bone medication use compared with men reporting no treatment with ADT, although there was a trend toward increased odds of fracture in this group when compared with men who did not receive any ADT (P = 0.08). Men
### Table 1. Baseline characteristics of men with localized prostate cancer by ADT treatment group

| N (%) | No ADT, N (%) | <1 Year ADT, N (%) | >1 Year ADT, N (%) |
|-------|---------------|--------------------|-------------------|
| Total | 961 (100)     | 684 (71.2)         | 120 (12.5)        | 157 (16.3)       |
| Age (in years) (at diagnosis) | | | | |
| <50 | 33 (3) | 28 (4) | 3 (3) | 2 (1) |
| 50–59 | 315 (33) | 238 (35) | 31 (26) | 46 (29) |
| 60–69 | 439 (46) | 315 (46) | 58 (46) | 66 (42) |
| 70–79 | 170 (18) | 102 (15) | 27 (23) | 41 (26) |
| ≥80 | 4 (0) | 1 (0) | 1 (1) | 2 (1) |
| Race | | | | |
| Non-Hispanic white | 725 (75) | 528 (77) | 91 (76) | 106 (68) |
| Non-Hispanic black | 115 (12) | 70 (10) | 15 (12) | 30 (19) |
| Hispanic | 121 (13) | 86 (13) | 14 (12) | 21 (13) |
| Marital status | | | | |
| Married | 848 (88) | 610 (89) | 109 (91) | 129 (82) |
| Unmarried | 108 (11) | 71 (10) | 11 (9) | 26 (17) |
| Unknown | 5 (1) | 3 (0) | 0 (0) | 2 (1) |
| Education level | | | | |
| Quartile 1 (<high school) | 111 (12) | 73 (11) | 20 (17) | 18 (11) |
| Quartile 2 (high school/some college) | 408 (43) | 276 (40) | 48 (40) | 84 (54) |
| Quartile 3 (college) | 174 (18) | 132 (19) | 24 (20) | 18 (11) |
| Quartile 4 (advanced degree) | 260 (27) | 198 (29) | 28 (23) | 34 (22) |
| Unknown/refused | 8 (1) | 5 (1) | 0 (0) | 3 (2) |
| Insurance | | | | |
| Medicare | 279 (29) | 187 (27) | 41 (34) | 51 (32) |
| Private or military | 572 (60) | 415 (61) | 66 (55) | 91 (58) |
| Medicaid or other | 18 (2) | 12 (2) | 4 (3) | 2 (1) |
| No insurance | 5 (1) | 4 (1) | 1 (1) | 0 (0) |
| Unknown/refused | 87 (9) | 66 (10) | 8 (7) | 13 (8) |
| Tumor grade (Gleason) | | | | |
| Gleason < 6 | 738 (77) | 553 (81) | 82 (68) | 103 (66) |
| Gleason 7 | 160 (17) | 100 (15) | 24 (20) | 36 (23) |
| Gleason ≥ 8 | 63 (7) | 31 (5) | 14 (12) | 18 (11) |
| Charlson comorbidity score | | | | |
| 0 | 465 (48) | 348 (51) | 49 (41) | 68 (43) |
| 1 | 317 (33) | 225 (33) | 45 (38) | 47 (30) |
| 2 | 123 (13) | 78 (11) | 14 (12) | 31 (20) |
| ≥ 3 | 56 (6) | 33 (5) | 12 (10) | 11 (7) |
| Baseline comorbid disease | | | | |
| Diabetes* | 64 (7) | 34 (5) | 15 (12) | 15 (10) |
| Congestive heart failure | 20 (2) | 13 (2) | 4 (3) | 3 (2) |
| Stroke | 20 (2) | 13 (2) | 2 (2) | 5 (3) |
| Heart attack | 45 (5) | 26 (4) | 10 (8) | 9 (6) |
| Hypertension | 285 (30) | 191 (28) | 39 (32) | 55 (35) |
| Chronic pulmonary disease | 16 (2) | 12 (2) | 1 (1) | 3 (2) |
| Depression* | 57 (6) | 28 (6) | 13 (11) | 6 (4) |

### Table 1. (Continued)

| N (%) | No ADT, N (%) | <1 Year ADT, N (%) | >1 Year ADT, N (%) |
|-------|---------------|--------------------|-------------------|
| Primary treatment | | | | |
| Radical prostatectomy | 697 (73) | 538 (79) | 78 (65) | 81 (52) |
| Radiation therapy | 158 (16) | 97 (14) | 27 (23) | 34 (22) |
| Hormonal therapy | 26 (3) | 0 (0) | 13 (11) | 13 (8) |
| Watchful waiting | 80 (8) | 49 (7) | 2 (2) | 29 (18) |

**Abbreviations:** ADT, androgen deprivation therapy; SEER, Surveillance, Epidemiology and End Results. *P*-value calculated by Pearson’s χ² test after collapsing neighboring categories to account for empty cells. **P*-value calculated by Pearson’s χ² test. *Diabetes (P = 0.003) and depression (P = 0.04) were the only baseline comorbidities that significantly varied in prevalence between ADT treatment groups. *P*-values calculated by Pearson’s χ² test (not shown). **Treatment groups were divided as follows: radical prostatectomy includes men who reported prostatectomy alone, prostatectomy plus radiation, prostatectomy plus hormonal therapy (ADT or orchiectomy) and prostatectomy plus radiation and hormonal therapy; radiation includes men who reported radiation alone, and radiation plus hormonal therapy; hormonal therapy includes only men who reported definitive hormonal therapy as their primary treatment; watchful waiting includes men who reported watchful waiting or no treatment.

### Table 2. Odds ratios for bone-related complications 15 years after diagnosis by ADT treatment group (univariable analysis)

| N/total | OR | 95% CI | P-value |
|---------|----|--------|---------|
| No ADT | 65/611 | Ref. | | |
| <1 year ADT | 11/107 | 0.97 | 0.5–1.9 | 0.92 |
| >1 year ADT | 23/125 | 1.7 | 1.0–2.9 | 0.04 |
| Bone mineral density testing | | | | |
| No ADT | 150/465 | Ref. | | |
| <1 year ADT | 34/76 | 1.4 | 0.9–2.2 | 0.15 |
| >1 year ADT | 77/52 | 4.6 | 3.1–6.8 | <0.001 |
| Bone medication use | | | | |
| No ADT | 169/495 | Ref. | | |
| <1 year ADT | 38/76 | 1.5 | 0.96–2.2 | 0.08 |
| >1 year ADT | 79/70 | 3.3 | 2.3–4.8 | <0.001 |

**Abbreviations:** ADT, androgen deprivation therapy; OR, odds ratio. *P*-value calculated by logistic regression. **Statistically significant result.

Reporting treatment with prolonged ADT had significantly increased risk of fracture (OR 2.5; 95% confidence interval (CI): 1.1–5.7) and bone medication use (OR 4.3; 95% CI 2.3–8.0) compared with men who denied treatment with ADT. BMD testing was more likely among men reporting treatment with both short-term and prolonged ADT than among men not reporting ADT treatment (OR 2.6, 95% CI: 1.2–5.8 for short-term ADT; OR 5.9, 95% CI: 3.0–12 for prolonged ADT). A sensitivity analysis performing the same analysis while excluding patients who experienced fracture yielded virtually identical results (data not shown).

Age, marital status, comorbidity and Gleason grade were not associated with risk of fracture at 15 years, but African Americans had a lower risk of fracture compared with Caucasians (OR 0.15; 95% CI: 0.04–0.60). Participants were more likely to report BMD testing as they aged (OR 1.5 per 10 years, P = 0.04), but less likely to report testing with increasing comorbid illness, with adjusted ORs of 0.18 (P < 0.001) for Charlson score 2 and 0.24 (P = 0.009) for Charlson score ≥ 3, using persons with a score of 0 as the reference group (data not shown). Compared with participants not
Americans may have a lower risk of fracture as compared with Caucasians after 2 years of treatment with ADT (2-year incidence of any fracture was 9.8% in Caucasian men and 2.9% in African-American men, \( P = 0.07 \)). Findings from the PCOS cohort provide much-needed prospective data and long-term follow-up to confirm previously reported findings from these short-term prospective studies and retrospective database analyses.

The frequency of BMD testing and factors that influenced testing differed in this study from previously reported SEER-Medicare analyses. Men treated with prolonged ADT in the PCOS received BMD testing more commonly than men treated with >1 year of ADT in the SEER-Medicare population (49% vs 10.2%). Frequency of BMD testing was also higher in the PCOS cohort overall (27%). In contrast to the SEER-Medicare analysis, men in the PCOS were more likely to report BMD testing as they aged, whereas men 85 years of age or older in the SEER-Medicare analysis were less likely to undergo BMD testing than men aged 66–69 years (OR 0.76; 95% CI: 0.65–0.89). These differences may be because of selection and response bias, as men choosing to participate in this study 15 years after their initial treatment for cancer may be more likely to engage in positive health-care behaviors and advocate for BMD testing as they age. This difference may also be because of regional variability detected in the SEER-Medicare analysis, as PCOS only sampled men from six of the available SEER regions. Importantly, the higher frequency of BMD testing in the aging PCOS cohort appears to reflect appropriate medical care, as a recent analysis found that the risk of fracture increases with age, with 98.8% of men over 80 years of age meeting the criteria for pharmacologic therapy for fracture prevention.

To the best of our knowledge, our analysis is the first to report that the use of bone medications was significantly more common among men treated with prolonged ADT compared with untreated men, possibly indicating that practitioners are increasingly implementing appropriate osteoporosis and fracture prevention strategies, and counseling these high-risk patients. The majority of men who reported use of bone medications used either calcium or vitamin D, both of which are easily accessible over the counter. The use of bisphosphonates for prevention of fragility fractures in prostate cancer survivors at high risk of fracture, recommended for several years before the administration of the 15-year survey, was less common. This may reflect poor understanding of the survey question by participants, slow uptake of national guideline recommendations or low estimation of patient fracture risk by providers.

Although our study reports multiple clinically relevant findings, we acknowledge that it has several limitations. First, the analysis cohort is approximately 27% of the original sample of men owing to death or drop out from the study, as described elsewhere. Because of this, the assessed cohort may represent a healthier ‘survivor’ cohort without high rates of bone complications, resulting in under-reporting of those rates. However, one may expect similar or greater numbers of ‘survivor’ participants in the no ADT or short-term ADT groups given their less aggressive prostate cancer, meaning the association demonstrated would bias toward the null. Second, we rely on patient report of long-term bone-related outcomes, possibly underestimating the frequency of fracture and BMD testing. Finally, our analysis does not reflect physician recommendations that may have been disregarded by patients with poor adherence. Despite these limitations, the noteworthy strengths of these data are the length of the follow-up period and the diverse population that included younger men and a substantial proportion of minorities.

**CONCLUSION**

Men treated with prolonged ADT had significantly higher odds of fracture over a 15-year period after diagnosis than men not treated with ADT. Men receiving prolonged ADT also reported

### Table 3. Multivariable analysis of the adjusted association between ADT duration and the development of fracture 15 years after diagnosis

| ADT duration          | OR  | 95% Confidence interval | P-value<sup>b</sup> |
|-----------------------|-----|-------------------------|---------------------|
| No ADT                |     |                         |                     |
| ❯1 year of ADT        | 2.5 | 0.9–7.0                 | 0.08                |
| >1 year of ADT        | 2.5 | 1.1–5.7                 | 0.033<sup>c</sup>   |
| Age at diagnosis (by 10 years) | 1.6 | 0.9–2.7                 | 0.10                |
| Race                  |     |                         |                     |
| Caucasian             |     |                         |                     |
| Black                 | 0.15| 0.04–0.6                | 0.008<sup>c</sup>   |
| Hispanic              | 1.0 | 0.5–2.3                 | 0.97                |
| Marital status        |     |                         |                     |
| Married               |     |                         |                     |
| Single                | 1.1 | 0.4–2.6                 | 0.88                |
| Comorbidity index     |     |                         |                     |
| 0                     |     |                         |                     |
| 1                     | 0.4 | 0.2–1.0                 | 0.05                |
| 2                     | 0.6 | 0.2–1.7                 | 0.33                |
| 3+                    | 0.8 | 0.1–5.0                 | 0.85                |
| Gleason score         |     |                         |                     |
| ◊6                    | 0.9 | 0.4–2.1                 | 0.84                |
| 8–10                  | 0.8 | 0.2–3.4                 | 0.79                |

Abbreviations: ADT, androgen deprivation therapy; OR, odds ratio. <sup>a</sup>Multivariable model adjusts for ADT treatment, age, race, marital status, comorbidity index and Gleason score. <sup>b</sup>P-value calculated by multivariable logistic regression incorporating sampling weights. <sup>c</sup>Statistically significant result.

**DISCUSSION**

Results from the PCOS provide important insights into the issue of bone health and patterns of preventive care in prostate cancer survivors who are receiving ADT. The odds of fracture, BMD testing and bone medication use were higher among men treated with prolonged (>1 year) ADT compared with men not receiving ADT. The corresponding associations for short-term ADT use (<1 year) were generally in the same direction, but far less pronounced.

Our data are consistent with several previously reported studies describing the effects of ADT on the risk of fracture. Several small prospective clinical trials with brief follow-up (12–24 months) demonstrate an association between exposure to ADT and declining BMD, but do not describe the long-term risk of fracture. This analysis demonstrated that men treated with ADT for more than 1 year had an increased risk of fracture compared with men not receiving treatment with ADT, whereas men treated with short-term ADT had a risk of fracture that was similar to that of untreated men. Although the rates of fracture were lower than those reported in fracture prevention trials that assess for asymptomatic fractures via scheduled skeletal surveys, the rate of fracture in this long-term, prospective study is consistent with evidence from previously reported Medicare analyses. Among various patient-related factors, only African-American race was associated with decreased odds of fracture (OR 0.15 compared with Caucasians), an observation that was consistent with a recent study that suggested that African American men, those with long-term ADT use had significantly increased likelihood of bone medication use with an adjusted OR of 4.3 (\( P < 0.001 \)). There were no significant associations between bone medication use and any other independent variables including age, marital status, comorbidity, race or Gleason grade (data not shown).

Exposed to ADT, those with long-term ADT use had significantly increased likelihood of bone medication use with an adjusted OR of 4.3 (\( P < 0.001 \)). There were no significant associations between bone medication use and any other independent variables including age, marital status, comorbidity, race or Gleason grade (data not shown).

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**CONCLUSION**

Men treated with prolonged ADT had significantly higher odds of fracture over a 15-year period after diagnosis than men not treated with ADT. Men receiving prolonged ADT also reported
more frequent screening and treatment for bone-related complications, with 50% reporting use of bone medications. Notably, men receiving short-term ADT had a similar risk of fracture to men not receiving ADT, suggesting that short durations of adjuvant ADT therapy may not appreciably increase the risk of this complication. African-American men reported fewer fractures, but underwent bone density testing at a similar frequency to Caucasian participants. Continued efforts to reduce skeletal complications for men receiving ADT should focus on reducing overtreatment of men with ADT when possible, and addressing skeletal health screening and complication prevention in men receiving prolonged ADT.

CONFLICT OF INTEREST
PCA has a compensated advisory role at Ferring Corporation. The other authors declare no conflict of interest.

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