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ORIGINAL REPORT

Timing of androgen deprivation therapy use and fracture risk among elderly men with prostate cancer in the United States

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ABSTRACT

Purpose Fractures are a recognized consequence of androgen deprivation therapy (ADT); however, less is known about the incidence of fracture in relation to the timing of ADT use or the impact of fracture on mortality in men with prostate cancer.

Methods Using data from the Surveillance, Epidemiology, and End Results–Medicare linked database, we estimated adjusted hazard ratios (aHRs) using time-dependent Cox regression for fracture incidence related to the recency of exposure and dose among prostate cancer patients on gonadotropin-releasing hormone (GnRH) agonists, as well as mortality associated with fractures.

Results In our cohort of 80 844 patients, ADT was associated with an increased rate of fracture in both non-metastatic patients (aHR = 1.34; 95% confidence interval [CI] = 1.29–1.39) and metastatic patients (aHR = 1.51; 95%CI = 1.36–1.67). Fracture rates increased with increasing cumulative GnRH dose but decreased with increasing number of months since last use in each dose category. The mortality rate doubled for men experiencing a fracture after their diagnosis compared with that for men who did not experience a fracture (aHR = 2.05; 95%CI = 1.98–2.12).

Conclusions ADT in elderly men with prostate cancer increased the incidence of fractures, and the effect appears to diminish with increasing time since the last dose of a GnRH agonist. Experiencing a fracture after the diagnosis of prostate cancer was associated with decreased survival.

KEY WORDS—epidemiology; prostate cancer; GnRH agonist; orchiectomy; SEER–Medicare; mortality; skeletal-related events

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INTRODUCTION

Androgen deprivation therapy (ADT) is a common treatment for men with metastatic prostate cancer, for those with non-metastatic disease in combination with radiation therapy, as well as among patients with rising prostate-specific antigen concentrations after definitive treatment (radical prostatectomy or radiation therapy).[1] With the rise in the use of ADT, there has been increasing recognition of potentially serious adverse effects including diabetes, cardiovascular disease, osteoporosis, and fracture.[2–5] It has been estimated that use of gonadotropin-releasing hormone (GnRH) agonists among men with non-metastatic prostate cancer is associated with an annual loss of 0.6% to 4.6% in bone mineral density, with the greatest rate of bone loss occurring during the first year of therapy.[1,6–8] Several lines of treatment have been shown to reverse ADT-related bone loss in patients with non-metastatic prostate cancer, including bisphosphonates, RANK ligand monoclonal antibodies, and selective estrogen receptor modulators.[9–15]

Although the association between ADT and fracture risk in prostate cancer has been established, [2,3,16–18] we know much less about how this risk varies as a

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function of duration of time on ADT and, for those who discontinue therapy, how risk varies with time since discontinuation. Furthermore, although ADT-induced skeletal complications clearly influence the quality of life in men with prostate cancer, a large-scale investigation of the potential impact of experiencing a fracture on mortality among men with non-metastatic disease has never been conducted.[1] In this investigation, using the most recent decade of data available from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, we estimate the incidence of fracture associated with both the recency of use and cumulative dose of ADT in men with prostate cancer. In addition, we estimate the relative risk of death among non-metastatic prostate cancer patients who experience a fracture.

METHODS

The SEER–Medicare dataset is a unique resource linking two population-based sources of data used to provide information about the experience of elderly patients with cancer in the USA. The SEER program, sponsored by the National Cancer Institute, is a network of population-based cancer registries that routinely collects information on patients with a new diagnosis of invasive cancer, residing within one of the registry catchment areas. SEER is composed of 18 statewide or regional cancer registries, collecting data on patient demographics, tumor histology and pathology, first course of treatment, and survival. Through linking SEER registry data to Medicare enrollment and claims files, the SEER–Medicare database provides additional information on treatment and outcomes of approximately 25% of elderly patients diagnosed with cancer in the USA.[19]

The eligible patients for the current investigation were diagnosed at the age of 66 years and older with primary malignant prostate cancer (site code C61.9, International Classification of Diseases for Oncology 3rd Edition) between 1 January 1996 and 31 December 2003, captured among 1 of 16 SEER registries (Connecticut, Hawaii, Iowa, New Mexico, Utah, Atlanta, Rural Georgia, Detroit, Seattle-Puget Sound, Los Angeles, San Jose-Monterey, San Francisco-Oakland, Greater California, Kentucky, Louisiana, and New Jersey). Patients not continuously enrolled in both Part A and Part B Medicare for the 12 months prior to and following prostate cancer diagnosis were excluded in an effort to minimize the misclassification of fracture as well as other comorbidities prior to prostate cancer diagnosis. Patients who were members of a health maintenance organization (HMO) at any point in the 12-month period prior to and following prostate cancer diagnosis were also excluded to avoid the potential for missing information due to claims not processed through Medicare. Patients receiving ADT prior to prostate cancer diagnosis were excluded, as well as patients with a fracture claim within 1 month of cancer diagnosis and those missing important clinical data, leaving a total study population of 80 844 men available for analysis (Figure 1).

Exposure to ADT was based on the documentation of at least one dose of a GnRH agonist or orchiectomy after prostate cancer diagnosis. To calculate GnRH dose, we used the methods developed by one of our coauthors (V.S.) as recommended by the National Cancer Institute (NCI).[2] Dose was calculated from each instance of a GnRH agonist injection noted on separate days for the 12-month period after diagnosis as well as the total number of doses over the follow-up period. Because GnRH agonists are administered as depot injections with the dosage given depending on the intended regimen (every 1, 3, and 4 months), the dosage recorded from the Medicare claims files was then converted to a once-a-month regimen. In addition, time (in months) since last use of a GnRH agonist was calculated from the month of last dose to the month of fracture or censoring.

Fracture diagnoses were identified through International Classification of Diseases, 9th revision (ICD-9) codes and extracted from the Medicare physician (carrier), inpatient, or outpatient claims files. Fractures requiring hospitalization were analyzed separately from inpatient claim files. Patients were followed for fracture until 31 December 2006, representing the end of complete follow-up for patients included in SEER–Medicare. Patient characteristics (age at diagnosis, race, and a history of osteoporosis, osteopenia, and fracture), year of diagnosis, disease characteristics (clinical tumor stage and histological grade), and treatment other than ADT (radical prostatectomy and radiation therapy) were examined for their relations with fracture incidence. We also included in our analyses a modified version of the Charlson comorbidity index, which was based on ICD-9 diagnostic and procedure codes as well as on the Healthcare Common Procedure Coding System codes for 10 conditions captured in the 12-month period prior to prostate cancer diagnosis for all cases.[20] Ecologic measures of socioeconomic position were also evaluated describing the education and income level of the census tract in which the patient resided at the time of diagnosis.[21]

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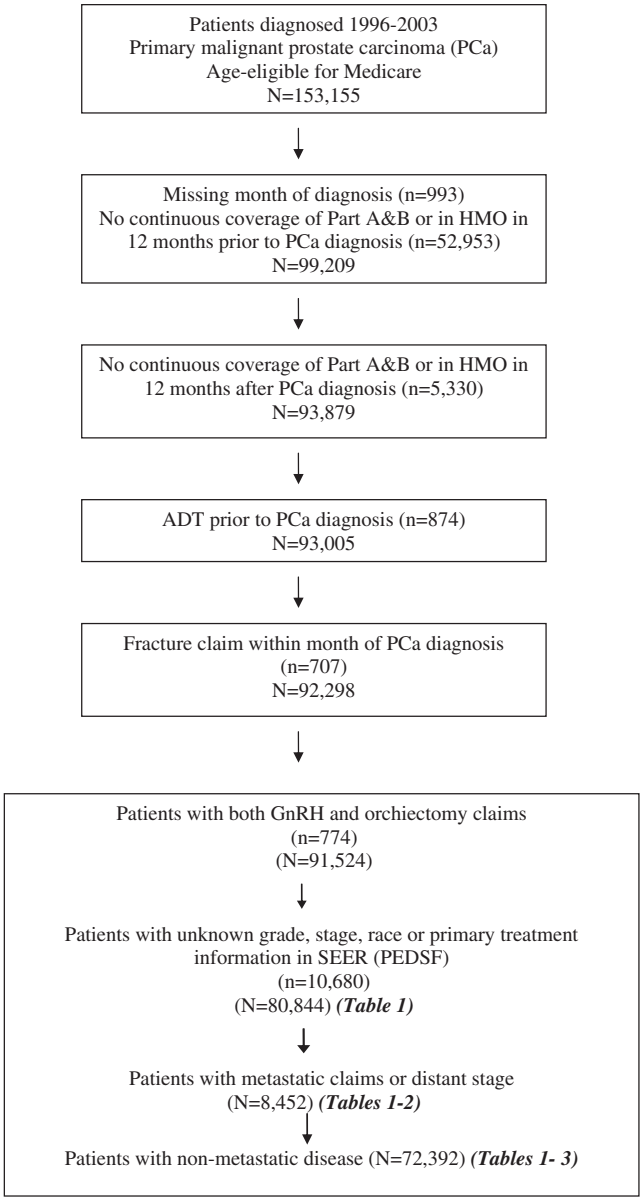

Figure 1. Prostate cancer patients participating in SEER–Medicare study

Statistical methods

All statistical analyses were performed using the Statistical Analysis Software (SAS Institute Inc. v. 9.1, Cary, NC). We calculated the proportion of patients receiving ADT as part of their treatment according to various baseline characteristics. We estimated both the incidence of fracture (with 95% confidence intervals [CIs]) for all patients combined and according to ADT treatment, standardized to the age distribution of non-ADT patients. Likewise, the estimated rate associated with ADT was calculated for the three most common sites of fracture (rib, hip, and spine). Cox proportional hazards regression was used to estimate adjusted hazard ratios (aHRs) and 95%CIs associated with ADT controlling for potential confounders. ADT was treated as a time-dependent covariate (i.e., patients were not considered exposed until the date of first receipt of a GnRH agonist or orchiectomy). The outcome was the time (in months) to fracture or censoring. Prostate cancer patients with no fracture claim during follow-up were censored at (i) death, (ii) loss of or change in Medicare coverage, or (iii) 31 December 2006—whichever came first. Final models

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included age at diagnosis, race, history of fracture, osteoporosis or osteopenia, Charlson comorbidity index, tumor grade, stage, primary treatment (radiation or prostatectomy), and use of intravenous (IV) bisphosphonates (among metastatic patients). Fracture analyses were further stratified to examine ADT effects separately among patients with and without metastatic disease, determined from data collected from either SEER or evidence of bone metastases extracted from claims files. When the findings related to ADT were similar in patients with and without metastatic disease, we opted to present only those findings for men with non-metastatic disease. However, when the findings were deemed different among men with metastatic disease, the aHRs are presented separately. To capture the effect of the timing of ADT and the cumulative dosage on fracture incidence, a time-dependent covariate was created that took into account the time from last treatment (TFLT) in months. The TFLT was equal to 0 if the patient was on ADT during the month of consideration and increased by one for each month off treatment unless treatment resumed, in which case TFLT once again equaled 0. This information was then combined with the cumulative (CUM) dosage of ADT up to the month of interest using methodology recommended to capture multiple characteristics of a single exposure.[22] For example, TFLT6CUM10 would indicate 6 months from the patient's last GnRH agonist dose, with a total of 10 doses at that particular point. We estimated hazard ratios for each combined exposure category relative to the reference group (men without ADT). Last, we used Cox regression to estimate the mortality rate associated with (i) any fracture and (ii) fracture requiring hospitalization, treating each as a time-dependent predictor, adjusting for potential confounders (i.e., age, race, year of diagnosis, tumor grade, stage, comorbidities, and primary treatment).

RESULTS

Of the 80 844 prostate cancer patients diagnosed at the age of 66 years and older included in this investigation, 14 905 (18.4%) experienced at least one fracture during the course of follow-up, with 3340 (4.1%) having a fracture that required hospitalization. Nearly 53% of patients in the study received some form of ADT after their prostate cancer diagnosis (Table 1), with 51% of patients on GnRH agonists and 2% of patients undergoing orchiectomy. ADT use was positively associated with age at diagnosis, with ~40% of patients aged 66 to 69 years receiving some form of ADT, compared with nearly 70% of patients diagnosed at the age of 80 years and older. The prevalence of use varied depending upon year of diagnosis, increasing from approximately 49% of patients diagnosed in 1996 to 57% of patients diagnosed in 2000, and then declining through 2003. ADT use was more common among patients with one or more conditions captured by the Charlson index, among patients with advanced stage and/or aggressive grade disease and, as expected, among patients electing radiation therapy as their primary treatment or no definitive treatment. The use of IV bisphosphonates prior to fracture in this population was low overall (2.3%) and differed by the presence of distant metastases (0.6% in non-metastatic patients and 18.2% in metastatic patients). This was expected given the timing of the study period relative to the approval of zoledronic acid by the US Food and Drug Administration for the treatment of bone metastases from solid tumors.[23]

The age-standardized incidence of fracture was higher among ADT users than that among non-users. The fracture rate among patients receiving at least one dose of a GnRH agonist was 57 per 1000 persons per year (95%CI = 56–58) compared with 31 per 1000 persons per year (95%CI = 30–32) among non-users. The fracture rate among orchiectomy patients was 76 per 1000 persons per year (95%CI = 68–84).

Among non-metastatic patients, GnRH agonist use, treated as a time-dependent dichotomous variable, was associated with a 34% increase in the rate of any fracture (HR = 1.34; 95%CI = 1.29–1.39), and a positive dose–response relation was observed between fracture incidence and the cumulative number of GnRH doses received over the study period (Table 2). A slightly higher increase in fracture incidence associated with ADT use was observed among men with metastatic disease (aHR = 1.51; 95%CI = 1.36–1.67). Again, aHRs increased with increasing GnRH dose. Orchiectomy was associated with a 62% increase in risk of any fracture (aHR = 1.62; 95%CI = 1.42–1.84) among non-metastatic patients and a 54% increase in risk among metastatic patients (aHR = 1.54; 95%CI = 1.26–1.88). The three most common sites of first-time fracture among patients in the study were rib (17.5%), hip (16.5%), and spine (14.6%), but the elevation in incidence associated with ADT use did not differ appreciably by site (data not shown).

Among non-metastatic patients using GnRH agonists, the incidence rate of fracture was positively associated with cumulative ADT dose and inversely related to the number of months since last use (Table 3). Thus, the fracture risk was highest among patients receiving at least 18 doses of an agonist who were either currently on or who had stopped

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Table 1. Frequency distributions of patient characteristics in SEER–Medicare study of androgen deprivation therapy and fracture risk in men with prostate cancer

	All			Non-metastatic			Metastatic		
Characteristic	*n*	(%)*	Proportion on ADT (%)	*n*	(%)*	Proportion on ADT (%)	*n*	(%)*	Proportion on ADT (%)
Total	80 844		52.8	72 392	89.5	49.9	8452	10.5	77.6
Age (in years)									
66–69	20 453	25.3	39.3	18 754	25.9	36.5	1699	20.1	70.2
70–74	26 418	32.7	49.7	23 782	32.9	47.0	2636	31.2	74.0
75–79	20 256	25.1	59.8	18 049	24.9	57.2	2207	26.1	80.6
≥ 80	13 717	17.0	68.5	11 807	16.3	65.7	1910	22.6	85.7
Race									
White	66 005	81.6	52.4	59 595	82.3	49.5	6410	75.8	79.2
Black	7478	9.2	50.5	6373	8.8	48.1	1105	13.1	64.3
Other	7361	9.1	58.1	6424	8.9	54.6	937	11.1	82.1
Year of diagnosis									
1996	6509	8.1	49.1	5391	7.4	44.5	1118	13.2	71.3
1997	6699	8.3	50.1	5641	7.8	46.1	1058	12.5	71.4
1998	6385	7.9	52.3	5518	7.6	48.9	867	10.3	73.6
1999	6965	8.6	53.9	6084	8.4	50.4	881	10.4	78.1
2000	12 638	15.6	56.6	11 342	15.7	53.6	1296	15.3	83.0
2001	13 763	17.0	54.5	12 565	17.4	51.9	1198	14.2	81.3
2002	14 393	17.8	52.1	13 294	18.4	49.7	1099	13.0	81.4
2003	13 492	16.7	50.8	12 557	17.3	48.7	935	11.1	78.7
<12 years of education†									
<10%	27 233	33.7	49.4	24 778	34.2	46.5	2455	29.0	79.3
10% to < 20%	28 312	35.0	53.6	25 385	35.1	50.7	2927	34.6	78.7
20% to < 30%	12 571	15.6	54.3	11 116	15.4	51.6	1455	17.2	74.4
≥ 30%	12 724	15.7	56.6	11 109	15.3	53.8	1615	19.1	76.0
Income below the poverty line†									
<3%	12 124	15.0	51.7	10 951	15.1	48.9	1173	13.9	77.6
3% to < 7%	26 469	32.7	52.4	23 802	32.9	49.5	2667	31.6	78.4
7% to < 14%	21 762	26.9	52.6	19 591	27.1	49.7	2171	25.7	78.7
≥14%	20 485	25.3	54.0	18 044	24.9	51.1	2441	28.9	75.8
Charlson comorbidity index									
0	59 617	73.7	50.9	53 429	73.8	47.8	6188	73.2	78.0
1	14 801	18.3	57.0	13 259	18.3	54.7	1542	18.2	76.0
2	4261	5.3	59.8	3792	5.2	57.4	469	5.5	79.1
+3	2166	2.7	60.4	1913	2.6	58.4	253	3.0	75.5
Grade of prostate cancer									
Well differentiated	4475	5.5	35.9	4225	5.8	34.7	250	3.0	56.0
Moderately differentiated	55 710	68.9	47.4	51 538	71.2	45.6	4172	49.4	69.7
Poorly differentiated	20 659	25.6	70.9	16 629	23.0	67.0	4030	47.7	87.1
Clinical T stage									
I	30 423	37.6	45.2	28 417	39.3	43.8	2006	23.7	66.1
II	45 526	56.3	54.5	41 938	57.9	52.6	3588	42.5	76.5
III	2009	2.5	79.8	1676	2.3	77.5	333	3.9	91.6
IV	2886	3.6	85.7	361	0.5	80.1	2525	29.9	86.5
SEER summary stage									
Local/Regional	78 382	97.0	51.7	72 392	100.0	49.9	5990	70.9	74.1
Distant	2462	3.0	86.2		0.0		2462	29.1	86.2
Other treatment within 6 months of diagnosis									
Neither	30 035	37.2	60.8	25 512	35.2	56.6	4523	53.5	84.2
Radiation	36 545	45.2	58.1	33 421	46.2	56.6	3124	37.0	74.6
Radical prostatectomy	13 605	16.8	20.8	12 885	17.8	19.2	720	8.5	48.6
Both	659	0.8	52.2	574	0.8	48.3	85	1.0	78.8

SEER, Surveillance, Epidemiology, and End Results; ADT, androgen deprivation therapy.
*Percentages may not sum 100% due to rounding.
†This refers to the census tract in which the patient resided at the time of diagnosis and the proportion of residents within the tract with fewer than 12 years of education or household income below the poverty line (four missing).

therapy in the past 6 months (compared with men who had not used ADT, aHR = 1.67; 95%CI = 1.56–1.78). Conversely, the fracture risk was almost the same for men who had received fewer than six doses more than 18 months ago and men who had not received any ADT (aHR = 1.06; 95%CI =

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Table 2. Adjusted hazard ratio* (and 95%CI) for fracture risk associated with ADT among elderly men diagnosed with prostate cancer ($n = 80\,844$)

	All fractures		Fractures requiring hospitalization	
	Non-metastatic	Metastatic	Non-metastatic	Metastatic
No ADT	1.00	1.00	1.00	1.00
Gonadotropin-releasing hormone agonist	1.34 (1.29–1.39)	1.51 (1.36–1.67)	1.34 (1.26–1.43)	1.58 (1.35–1.85)
1–5 doses†	1.21 (1.15–1.27)	1.22 (1.07–1.39)	1.11 (1.02–1.22)	1.12 (0.90–1.40)
6–17 doses	1.31 (1.25–1.38)	1.48 (1.31–1.68)	1.29 (1.19–1.40)	1.49 (1.24–1.81)
≥ 18 doses	1.66 (1.57–1.76)	1.99 (1.75–2.27)	1.74 (1.59–1.90)	2.20 (1.82–2.67)
Orchiectomy	1.62 (1.42–1.84)	1.54 (1.26–1.88)	1.87 (1.56–2.25)	1.63 (1.21–2.18)

CI, confidence interval; ADT, androgen deprivation therapy.
*Hazard ratios were adjusted for age at prostate cancer diagnosis, race, tumor grade, clinical T stage, presence of comorbidities, history of fracture, osteoporosis or osteopenia prior to prostate cancer diagnosis, and primary treatment. Analyses among metastatic patients were additionally adjusted for intravenous bisphosphonate use.
†Cumulative dose from diagnosis until fracture or censoring event.

Table 3. Risk of fracture associated with dose and recency of GnRH agonist use among men with non-metastatic prostate cancer ($n = 72\,392$)

	Months since last GnRH agonist dose			
	0–6 months	7–12 months	13–18 months	≥19 months
Cumulative dose	aHR (95%CI)	aHR (95%CI)	aHR (95%CI)	aHR (%%CI)
1–5 doses	1.43 (1.32–1.56)	1.26 (1.08–1.46)	1.24 (1.06–1.45)	1.06 (0.99–1.14)
6–17 doses	1.58 (1.47–1.69)	1.46 (1.28–1.65)	1.16 (1.00–1.35)	1.04 (0.96–1.13)
≥ 18 doses	1.67 (1.56–1.78)	1.58 (1.33–1.87)	1.62 (1.32–2.01)	1.36 (1.16–1.58)

GnRH, gonadotropin-releasing hormone; aHR, adjusted hazard ratio; CI, confidence interval.
aHR: hazard ratio using Cox regression adjusting for age at diagnosis, race, history of bone-related complications, presence of comorbidities, tumor grade, clinical T stage, and primary treatment.
*Referent group: patients not receiving any androgen deprivation therapy.

0.99–1.14). Similar trends were observed among metastatic patients (data not shown).

Among men with non-metastatic disease, the mortality risks within 6 and 12 months of experiencing any fracture were 8.3% and 12.2%, respectively. Fracture was associated with a more than twofold increase in the rate of death (aHR = 2.05; 95%CI = 1.98–2.12) after adjusting for age at diagnosis, year of diagnosis, race, the presence of one or more comorbidities prior to diagnosis, tumor grade, stage, and initial treatment. The occurrence of a fracture that required hospitalization was associated with a nearly threefold increase in the rate of death (aHR = 2.82; 95%CI = 2.68–2.97) after adjusting for the same prognostic covariates.

DISCUSSION

In this large, population-based investigation of elderly men with prostate cancer, we observed that the use of ADT was associated with a 34% increase in fracture incidence and that the rate increased with cumulative dose (among men on GnRH agonists). Our results are consistent with prior reports linking ADT to fracture in men with prostate cancer.[2,3,16] Our study is the first to report an inverse relationship between rate of fracture and the time since last use of GnRH agonists. In addition, we found that fracture occurrence after prostate cancer diagnosis was associated with excess mortality among men with non-metastatic disease, particularly when that fracture resulted in hospitalization.

Recent concepts about osteoporotic fracture incorporate the effect of increased bone turnover on impairment of bone strength, independent of reduced bone mineral density.[24] This is supported by results of trials of antiresorptive therapies in postmenopausal women that demonstrated fracture risk reduction that could not be fully explained by improvements in bone mineral density.[25] Androgen deprivation, through the induction of testosterone, and more importantly, estrogen deficiency, increases bone turnover and bone resorption, eventually leading to declines in bone mineral density.[26,27] Our findings are consistent with this current understanding of the pathophysiology of osteoporotic fracture risk. The increased rate of fracture in men receiving only a few doses of GnRH agonists, which then returns to normal over time after discontinuation of therapy, may predominantly represent the effect of androgen deprivation on bone turnover. In

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contrast, the even higher fracture rate in men on long-term therapy, which persists after discontinuation, may represent the additional effect of a profound reduction in bone mineral density.

There is still controversy about whether to prescribe long-term (2 to 3 years) or shorter (6 month) courses for men with locally advanced or high-risk disease with an indication for adjuvant ADT coupled with radiotherapy. Although in the clinical trial setting a longer duration of ADT leads to better overall and prostate-cancer-specific survival,[28] our findings suggest that it would also be associated with a higher and persistent risk of fracture, as compared with a shorter course of therapy. Because even short courses of adjuvant ADT with radiation improve overall and prostate-cancer-specific survival,[29] men with a medical history that places them at a high risk of fracture may wish to consider shorter courses of ADT to limit that risk.

The excess in the death rates observed among men with non-metastatic prostate cancer who experience a fracture is consistent with other hospital- and population-based investigations of fracture and mortality.[30–35] The incidence of hip fracture in the Medicare population has declined among men in the past decade, as has its associated mortality.[36] However, both the absolute and relative mortality risk rates associated with hip fracture are higher among men compared with women.[30,33,34] Risk of death is greatest in the days and weeks following fracture; however, it can remain elevated for months and even years.[30,31] There is continued concern about increased mortality due to non-prostate-cancer-related causes among patients on ADT, particularly among men with a history of cardiovascular disease.[37–39] Our results indicate that fracture also contributes to the excess in non-cancer mortality.

There are limitations worth noting in the current investigation. Confounding by indication is an important concern in observational studies examining the effect of treatment on an outcome.[40] Our findings indicate that ADT was used more frequently among prostate cancer patients with aggressive-grade and distant-stage disease. Because the presence of bony metastases increases fracture risk independently of treatment,[41] we stratified analyses and examined the associations with ADT separately among patients with and without evidence of metastatic disease, either at the time of diagnosis or at any point over follow-up. The observed hazard ratios associated with use of GnRH agonists were similar between groups for both any fracture and hospitalized fractures. In addition, the potential for residual confounding is an important consideration stemming from the observational nature of the investigation and the lack of complete information on all confounding factors. Therefore, our adjustment for comorbidities and available confounding variables in the analysis is likely incomplete.

Medicare data are limited to some degree due to the potential for missing information on services that are either not covered by Medicare or not billed to Medicare. For this reason, we excluded patients participating in an HMO in the 12 months prior to diagnosis and censored patients at the time of any change or loss in Medicare coverage over the course of study. The exclusion of HMO enrollees may limit the generalizability of our findings because HMO enrollees tend to be younger and healthier than Medicare beneficiaries.[42] A comparison of the baseline characteristics of patients excluded for incomplete Medicare coverage with those included in the analysis indicated that distributions were similar between groups (results not shown). An assessment of the representativeness of SEER patients included in the SEER–Medicare database with the elderly US population indicates that although the age and gender distribution is comparable, a greater proportion of SEER–Medicare patients belong to other minority (non-Black, non-White) groups and reside in urban areas.[42] Last, these findings are not necessarily generalizable to patients diagnosed with prostate cancer before the age of 65 years.

CONCLUSIONS

This study reconfirms the link between ADT and fracture incidence in elderly men with prostate cancer. Moreover, our results also indicate a reduction in fracture rates with an increasing amount of time since last use, irrespective of the cumulative dose, among men on GnRH agonists. Because our investigation also shows an association between fracture and mortality in these men, it is particularly important for clinicians to communicate the benefits and possible risks of androgen deprivation to patients and review strategies to reduce the potential adverse consequences of therapy.

CONFLICT OF INTEREST

Amgen Inc. provided the funds to support this research project. This project was intended to fill a gap in the published literature describing the burden of fracture among elderly men with prostate cancer and associated mortality. Dr. Acquavella and Ms. Cetin (employees of the sponsor), acting as collaborators on the study, were involved in the design, analysis, and interpretation of the data and in the writing of the article.

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KEY POINTS

- Fracture is a recognized consequence of ADT use; however, the mortality risk associated with fracture in men with prostate cancer has never been estimated in a large-scale investigation.
- Conditional on cumulative dose, the risk of fracture associated with ADT use in elderly men with prostate cancer declines with an increasing number of months since last use of a GnRH agonist, a finding not previously reported.
- Our findings suggest that careful monitoring of elderly patients on ADT is crucial, and continuous, long-term use may have serious adverse consequences for these men.

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