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Bone Density Testing Among Prostate Cancer Survivors Treated with Androgen Deprivation Therapy

Alicia K. Morgans, M.D., **Matthew R. Smith, M.D., Ph.D.**, **A. James O'Malley, Ph.D.**, and **Nancy L. Keating, M.D., M.P.H.**
Division of Hematology and Oncology, Massachusetts General Hospital (AKM and MRS), the Department of Health Care Policy, Harvard Medical School (AJO, NLK), and the Division of General Internal Medicine, Department of Medicine, Brigham and Women's Hospital (NLK), all in Boston, MA.

Abstract

Purpose—Androgen deprivation therapy (ADT) causes bone loss and fractures. Guidelines recommend bone density testing before and during ADT to characterize fracture risk. We assessed bone density testing among men receiving ADT for at least 1 year.

Materials and Methods—Using Surveillance, Epidemiology, and End Results-Medicare data, we identified 28,960 men aged >65 with local/regional prostate cancer diagnosed during 2001–2007 and followed through 2009 who received ≥1 year of continuous ADT. We documented bone density testing in the 18-month period beginning 6 months before ADT initiation. We used logistic regression to identify factors associated with bone density testing.

Results—Among men receiving ≥1 year of ADT, 10.2% had a bone density assessment from 6 months before starting ADT through 1 year after. Bone density testing increased over time (14.5% of men initiating ADT in 2007–2009 vs 6.0% in 2001–2002, OR=2.29, 95% CI=1.83–2.85). Less bone density testing was observed for men aged ≥85 (vs. 66–69, OR=0.76, 95% CI=0.65–0.89), black vs. white men (OR=0.72, 95% CI=0.61–0.86), and men in areas with lower educational attainment (P<.001). Men seeing a medical oncologist and/or a primary care provider in addition to a urologist had higher odds of testing than men seeing only a urologist (P<.001).

Conclusions—Few men receiving ADT for prostate cancer undergo bone density testing, particularly older men, black men, and those living in areas with low educational attainment. Visits with a medical oncologist were associated with increased odds of testing. Interventions are needed to increase bone density testing among men receiving long-term ADT.

Keywords

prostate cancer; caner survivorship; male osteoporosis; androgen deprivation therapy; side effects of treatment

Introduction

Prostate cancer remains the most commonly diagnosed non-cutaneous cancer in men in the United States.[1] Although it is also the second leading cause of cancer death in men, most

Address correspondence and reprint requests to: Nancy L. Keating, M.D., M.P.H., Department of Health Care Policy, Harvard Medical School, 180 Longwood Avenue, Boston, MA 02115. Phone: (617) 432-3093, Fax: (617) 432-0173, keating@hcp.med.harvard.edu.

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patients with prostate cancer become long term survivors of the disease. Because of this, awareness of late complications of therapy is critical in treating men with prostate cancer.

Androgen deprivation therapy (ADT) is the most frequently used systemic therapy for men with prostate cancer. Up to 50% of men with prostate cancer are treated with ADT during the course of their disease, and an estimated 600,000 American men with prostate cancer are receiving treatment with ADT at any given time.[2,3] ADT improves overall survival when given as adjuvant therapy for men with high-risk tumors and quality of life among men with metastatic prostate cancer. However, its use is increasing in other settings, for which benefits of treatment are less clear.

Although it is not as obviously toxic as chemotherapy, ADT is not without drawbacks.[4] ADT causes a decline in bone mineral density and increases the risk of treatment-related fragility fractures.[5–10] Since 2008, guidelines of the National Comprehensive Cancer Network (NCCN) have recommended routine bone density testing before and during treatment with ADT to characterize a man's fracture risk.[11] Additionally, the American College of Physicians (ACP) 2008 guidelines for male osteoporosis screening recommended bone density testing for all men at increased risk of developing osteoporosis, including men treated with ADT.[12]

Relatively few data are available describing rates of bone density testing among men receiving ADT. Several single institution studies of Veteran's Health Administration practices have reported low rates of bone density testing in men receiving ADT, even in subgroups at increased risk of developing osteoporosis and fragility fracture.[13–15] Frequency of bone density testing in men with prostate cancer treated in non-military institutions in the United States has not been reported.

In this analysis, we assessed bone density testing in a large, population-based cohort of older men with prostate cancer in the United States treated continuously with ADT for at least one year. We also identified patient, physician, and disease factors associated with testing.

Materials and Methods

Data

We used Surveillance, Epidemiology and End Results (SEER) Medicare data for this analysis. The SEER program of the National Cancer Institute collects uniformly reported data from population-based cancer registries covering approximately 28% of the United States population.[16] The information collected includes patient demographics, tumor characteristics, and treatment with surgery or radiation for each incident cancer.

Since 1991 SEER data have been merged with Medicare administrative data using a matching algorithm that successfully links files for over 94% of SEER patients aged 65 or older.[17] The Medicare claims data used in this study included the Medicare Provider Analysis and Review (MEDPAR) file (to identify inpatient admissions), the 100% Physician/Supplier file (to identify physicians' services for comorbidity assessment and ascertainment of bone density testing and androgen deprivation therapy), and the Hospital Outpatient Standard Analytic file (for outpatient facility services to identify comorbidity and bone density testing and androgen deprivation therapy).

Study Cohort

We identified all men with non-metastatic prostate cancer diagnosed from 2001–2007 who were aged 66 or older at diagnosis and enrolled in parts A and B of fee-for-service Medicare as of 1 year before diagnosis through 6 months after diagnosis (N=136,066). Men with

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metastatic disease were excluded as bone density testing with DXA is not reliable in bone with metastatic lesions. We excluded 1,817 men who were diagnosed at autopsy and 3,261 men with no claims from 45 days before diagnosis through 195 days after diagnosis (suggesting incomplete data). We then restricted to 118,839 men with locoregional prostate cancer who were followed through 2009. Among these men, we identified 29,860 who were treated continuously with ADT for at least 1 year. ADT was ascertained based on claims for GnRH agonists or bilateral orchiectomy (Current Procedural Terminology (CPT) codes 54520, 54521, 54522, 54530, 54535, 54690, 49510; International Classification of Disease, 9th Edition (ICD-9) Procedure codes 62.3, 62.4, 62.41, 62.42; Healthcare Common Procedure Coding System codes J9217, J9218, J9219, J1950). Men were considered hypogonadal for 6 months following the date of their last injection with GnRH agonist therapy because treatment effects are known to persist for prolonged periods; thus a man who received 6 months of adjuvant ADT (for example, with two 3-month depot injections of ADT) would be considered on therapy for 9 months, and would not be included in these analyses.

Bone Density Testing

We assessed receipt of bone density testing, including testing with DXA, ultrasound, and CT bone density testing in the 18-month period from 6 months before the first dose of ADT through a one year period following initiation of ADT (Current Procedural Terminology (CPT) codes 76070, 76071, 76075, 76076, 76077, 76078, 76977, 77078, 77079, 77080, 77081, 77082, 77083, 78350, 78351; International Classification of Disease, 9th Edition (ICD-9) Procedure codes 88.98; Healthcare Common Procedure Coding System codes G0130; International Classification of Disease, 9th Edition (ICD-9) Diagnosis codes V82.81).

Patient Characteristics

We characterized patients' age, race/ethnicity, marital status, urban residence, SEER region, comorbid illness at the time of initiation of ADT (based on the Klabunde modification of the Charlson Index[18,19]), year of initiation of ADT, tumor grade (by Gleason score), primary treatment (surgery, radiation, or neither), median household income and proportion of high school graduates in the census tract of residence (categorized in quartiles within registries), and hospitalizations in the year after starting ADT. We also characterized visits with physicians in the year after starting ADT, focusing on urologists, medical oncologists, and primary care physicians (PCP), defined as general internists, family practitioners, general practitioners, and geriatricians. Variables were categorized as in Table 1. Notably, nearly all men included in this study saw a urologist in addition to the other providers being assessed.

Analyses

We described receipt of bone density testing from the 6 months before the first dose of ADT through 12 months after the first dose by patient characteristics. We then used multivariable logistic regression with generalized estimating equations (to account for clustering by registry) to assess the association of patient and tumor characteristics, visits with physicians and hospitalizations on receipt of bone density testing. Independent variables included all variables in the Table.

All tests of statistical significance were two sided. We used SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina) for analyses. The study was approved by the institutional review boards at Harvard Medical School (Boston, MA) and Massachusetts General Hospital (Boston, MA).

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Results

Characteristics of the 28,960 men with locoregional prostate cancer who were treated with ADT for at least one year are included in the Table. Overall, 10.2% of these men underwent bone density testing during the period from 6 months before through one year after initiation of ADT.

Unadjusted rates of bone density testing by patient characteristics are presented in the Table, as are adjusted odds ratios [OR] and 95% confidence intervals [CIs]. Rates of bone density testing increased over time, with 14.5% of men initiating ADT from 2007–2009 undergoing testing vs. 6.0% of men initiating ADT in 2001–2002 (OR 2.29, 95% CI 1.83–2.85). Men ≥85 years old were less likely than men aged 66–69 years old to undergo bone density testing (OR 0.76, 95% CI 0.65–0.89). Black men were less likely than white men to undergo testing (OR 0.72, 95% CI 0.61–0.86) and men who were not black or Hispanic had higher rates of testing than white men (OR 1.39, 95% CI 1.13–1.71). Men living in areas with higher educational attainment were more likely to undergo bone density testing than those in areas with the lowest education levels. Unmarried men were less likely to have bone density testing than married men (OR 0.82, 95% CI 0.72–0.93). Bone density testing was more frequent in men with two or more (vs. none) comorbid medical conditions. Testing also varied substantially by region, with highest rates in Los Angeles and Hawaii and the lowest rates in Iowa and Connecticut.

The types of physicians with whom patients had visits were also associated with bone density screening. Men with a medical oncologist or PCP or both involved in their care were more likely to undergo testing than those who saw a urologist but no medical oncologist or PCP (Table), with the highest odds of bone density testing for men who saw a urologist, medical oncologist and primary care physician. Hospitalization during the year following initiation of ADT was not associated with receipt of bone density testing.

Discussion

We examined bone density screening for a large population-based cohort of older men in the United States who were diagnosed with locoregional prostate cancer and treated with ADT for at least one year and found that only 10.2% of these men received bone density testing between 6 months before and 12 months after ADT initiation. Rates of bone density testing increased over time, although still only 14.5% of men initiating ADT between 2007 and 2009 underwent testing, despite guideline recommendations for testing that were published in 2008.[11,12] Several populations of men, including black and elderly men, were significantly less likely than other men to undergo bone density testing. Treatment by a medical oncologist or PCP in addition to other providers was associated with higher likelihood of bone density testing. Of note, men with metastatic disease were omitted from these analyses as bone density testing with DXA is not reliable in bone with metastatic lesions. Additionally, men with metastatic disease are likely already being treated with bisphosphonates or other medications that have proven benefit in preventing skeletal related events in this population.

Our finding of low rates of bone density testing in prostate cancer survivors treated with ADT is consistent with previously reported evidence. Several small single-institution studies in Veteran's Health Administration settings found that between 8.7% and 14% of men receiving treatment with ADT for prostate cancer that varied by disease stage underwent bone density testing.[13–15] Another recent study of men receiving at least 6 months of ADT for prostate cancer in Ontario, Canada found rates of bone density testing in the 2 years after ADT initiation that ranged from a low of 0.5 per 100 person-years in 1995 to 18 per 100

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person-years in 2008 [20]. The lower rates of testing in our study are likely related to our assessing bone density testing through 12 months after ADT initiation, rather than 24 months, although differences in the U.S. vs. Canadian health care systems may have also contributed.

Our observation that African American men had lower rates of bone density testing than white men may result from physicians' awareness that African American men generally have higher baseline BMD than Caucasian men.[21, 22] However, despite starting with a higher baseline BMD, African American men and Caucasian men on ADT lose BMD at an equivalent rate.[23] Consistent with this, guidelines suggest that all men treated with ADT undergo baseline and subsequent bone density testing to assist in determining whether pharmacologic therapy to increase BMD is necessary.[24]

Men over 85 years of age were also less likely to undergo bone density testing in this analysis. This finding is consistent with other evidence suggesting less bone density testing in other settings as patients age[25]. However, risk for fracture increases with increasing age. A recent study found that 98.8% of men over age 80 met criteria for treatment of bone loss to prevent fracture based on recommendation for treating individuals who meet the World Health Orgainzation Fracture Risk Assessment (FRAX) algorithm treatment threshold.[26,27] It is possible that we observed lower rates of bone density testing in this group because physicians assumed they should be treated for osteoporosis based on age and use of ADT alone, obviating the need for additional radiographic data. We lacked data on oral medications to assess if patients were being treated with bisphosphonate therapy. An alternate explanation is that physicians recommend less bone density testing for older men because they perceive lower benefits to screening. It is also possible that physicians recommended testing, but patients elected not to undergo testing.

Unmarried men and men living in areas with lower educational attainment were less likely than married men to undergo bone density testing. It is generally recognized that married men's health behaviors are significantly influenced by their spouses, and unmarried men with prostate cancer have poorer overall survival.[28] Our finding may reflect unmarried men not receiving additional encouragement to access health care resources in general. Lower rates of bone density testing in men living in areas with lower educational attainment may reflect the challenges of communicating benefits of testing to men with less education or lower health literacy. Additional resources may be needed to improve communication with such populations about the benefits of testing.

Treatment by a medical oncologist and/or a PCP versus a urologist without either of these providers was associated with higher rates of bone density testing. Medical oncologists and primary care providers may be more attuned to issues such as osteoporosis prevention than urologists. Alternatively, this finding may reflect differences in the patients who seek care from multiple providers, who may differ from individuals who receive care from a single health care provider. These men may have more time available for additional physician visits and testing and may acquire more knowledge about risks of treatments due to care from an interdisciplinary team. In addition, guidelines recommending routine use of bone density testing before and during treatment with ADT are published by the NCCN and the American College of Physicians, and may be more commonly utilized by medical oncologists and PCPs than urologists.

Men with more comorbidities were more likely to undergo bone density testing than those who had no comorbidities. Similar to those men who have multiple practitioners involved in their cancer care, men with more comorbidities may have more opportunities for identifying a need for testing.

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It is notable that some factors we investigated were not associated with receipt of bone density testing in our study, including tumor grade, primary treatment, area-level income, and urban/rural status, although we observed large variations by SEER area. Unlike an analysis of bone density testing in one study of men treated in a Veteran's Health Administration hospital, Hispanic ethnicity was not associated with bone density testing in our study.[15]

Evidence about the adverse effects of ADT on skeletal health has been available for almost a decade, and since 2008, bone density testing has been recommended by the NCCN.[11,24] A recent study found that bone density testing to guide treatment with bisphosphonates in men receiving ADT for localized prostate cancer is a cost effective approach to this aspect of survivorship care.[29] As efforts to improve the delivery of cost-effective preventive care increase, measuring and incenting use of bone density testing for this population could be an effective strategy.

Our study has some limitations. First, our time period started before evidence about ADT-associated bone loss was widely available and ended in 2009. Thus low rates of bone density testing in the early years of this analysis may be explained by limited knowledge by practitioners. However, a lack of available guidelines does not completely explain low rates of testing as rates of testing remained low throughout the study period even after guidelines had been published. Second, we lacked information about physicians' recommendations for testing, and could only observe if testing was received. Third, we studied only older men living in SEER areas; testing patterns may differ among younger men or men in other parts of the U.S.

Conclusions

Few prostate cancer survivors treated with long-term ADT undergo bone density testing, and several key populations, including African Americans and older men, have considerably lower rates of bone density screening. Additional efforts are needed to increase screening for treatment-associated osteoporosis to prevent fractures in these men.

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Definitions

ADT	Androgen deprivation therapy
DXA	Dual energy x-ray absorptiometry
NCCN	National Comprehensive Cancer Network
PCP	Primary care physician
SEER	Surveillance, Epidemiology and End Results

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Table

Patient characteristics and receipt of bone density testing from 6 months before first dose of ADT through 1 year after

	N (%)	% who received bone density testing	P value*	Adjusted Odds Ratio	95% Confidence Interval	P value**
Total	28,960 (100)	10.2				
Age in years			.003			
66–69	4304 (15)	10.9		1.00		Ref
70–74	7224 (25)	10.5		0.99	0.86–1.13	0.88
75–79	8167 (28)	10.1		0.96	0.86–1.07	0.43
80–84	6119 (21)	10.6		0.98	0.84–1.14	0.76
≥85	3146 (11)	8.3		0.76	0.65–0.89	<0.001
Race			<.001			
Non-Hispanic white	22,115 (76)	10.1		1.00		Ref
Non-Hispanic black	2710 (9)	6.5		0.72	0.61–0.86	<0.001
Hispanic	1763 (6)	11.2		0.96	0.80–1.15	0.65
Other	1314 (5)	16.4		1.39	1.13–1.71	0.002
Unknown	1058 (4)	12.6		0.97	0.83–1.13	0.69
Marital status			<.001			
Married	18132 (63)	10.7		1.00		Ref
Unmarried	6084 (21)	8.3		0.82	0.72–0.93	0.002
Unknown	4744 (16)	10.9		1.07	0.92–1.24	0.41
Year initiating ADT			<.001			
2001–2002	8151 (28)	6.0		1.00		Ref
2003–2004	9002 (31)	9.3		1.50	1.13–1.71	<0.001
2005–2006	7088 (24)	13.6		2.22	1.76–2.79	<0.001
2007–2009	4719 (16)	14.5		2.29	1.83–2.85	<0.001
Residence			<.001			
Major metro area	15760 (54)	11.4		1.00		Ref
Metropolitan county	8223 (28)	10.2		1.10	0.87–1.41	0.43
Urban	1815 (6)	8.2		0.98	0.76–1.27	0.90
Less urban	2619 (9)	5.8		0.93	0.72–1.20	0.60
Rural	543 (2)	6.3		1.07	0.79–1.46	0.65

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	N (%)	% who received bone density testing	P value*	Adjusted Odds Ratio	95% Confidence Interval	P value**
SEER region			<.001			
Los Angeles	2152 (7)	17.1		1.00		Ref
San Francisco	750 (3)	11.7		0.59	0.57–0.61	<0.001
Connecticut	1840 (6)	7.0		0.36	0.31–0.42	<0.001
Detroit	2493 (9)	12.7		0.77	0.74–0.81	<0.001
Hawaii	576 (2)	14.6		0.61	0.47–0.80	<0.001
Iowa	2085 (7)	5.0		0.27	0.23–0.33	<0.001
New Mexico	539 (2)	12.6		0.69	0.58–0.81	<0.001
Seattle	1259 (4)	10.8		0.53	0.49–0.58	<0.001
Utah	644 (2)	9.0		0.45	0.38–0.54	<0.001
Atlanta	453 (2)	8.2		0.42	0.39–0.45	<0.001
San Jose/Monterey	812 (3)	11.1		0.58	0.51–0.66	<0.001
Rural Georgia	62 (<1)	***		0.19	0.15–0.24	<0.001
Great California	4569 (16)	13.9		0.77	0.70–0.85	<0.001
Kentucky	2104 (7)	6.4		0.35	0.31–0.39	<0.001
Louisiana	2587 (9)	6.3		0.38	0.32–0.44	<0.001
New Jersey	6035 (21)	9.1		0.53	0.51–0.55	<0.001
Median household income in census tract of residence			<.001			
Quartile 1 (lowest)	8269 (28)	9.0		1.00		Ref
Quartile 2	7563 (26)	9.6		0.93	0.84–1.04	0.20
Quartile 3	6833 (24)	10.0		0.89	0.77–1.02	0.10
Quartile 4 (highest)	6253 (22)	13.0		1.06	0.90–1.25	0.51
Unknown	42 (<1)	***		0.90	0.28–2.83	0.85
% high school graduates in census tract of residence			<.001			
Quartile 1 (lowest)	8201 (28)	8.5		1.00		Ref
Quartile 2	7388 (26)	9.4		1.13	1.02–1.25	0.02
Quartile 3	7143 (25)	10.9		1.30	1.14–1.49	<0.001
Quartile 4 (highest)	6186 (21)	12.8		1.44	1.25–1.66	<0.001
Unknown	42 (<1)	***		0.90	0.28–2.83	0.85
Tumor grade (Gleason)			<.001			
Well differentiated (2–4)	384 (1)	7.8		1.00		Ref

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	N (%)	% who received bone density testing	P value*	Adjusted Odds Ratio	95% Confidence Interval	P value**
Moderately differentiated (5–7)	11973 (41)	8.6		0.97	0.70–1.33	0.84
Poorly differentiated/undifferentiated (8–10)	15907 (55)	11.6		1.08	0.74–1.58	0.70
Unknown	696 (2)	8.8		1.01	0.57–1.81	0.97
Charlson comorbidity score			0.04			
0	18791 (65)	9.9		1.00		Ref
1	6451 (22)	10.5		1.09	0.99–1.20	0.08
2	2304 (8)	11.6		1.22	1.04–1.43	0.01
≥3	1414 (5)	11.0		1.13	1.02–1.25	0.02
Primary treatment received in the 6 months after diagnosis			<.001			
Radical prostatectomy	1033 (4)	15.0		1.25	0.92–1.68	0.15
Radiation therapy	13324 (46)	10.6		0.99	0.89–1.10	0.86
Neither	14603 (50)	9.6		1.00		Ref
Physicians seen in period from 6 months before through 12 months after first ADT dose			<.001			
Urologist, no PCP or medical oncologist	4333 (15)	6.5		1.00		Ref
Urologist and PCP, no medical oncologist	19937 (69)	9.4		1.42	1.18–1.72	<0.001
Urologist, PCP, and medical oncologist	3107 (11)	18.4		2.59	2.01–3.34	<0.001
Urologist and medical oncologist, no PCP	657 (2)	14.6		2.11	1.39–3.21	<0.001
No urologist, PCP or medical oncologist	926 (3)	14.7		1.94	1.46–2.58	<0.001
Hospitalizations			.63			
None	18694 (65)	10.3		1.00		Ref
1 or more	10266 (35)	10.1		0.97	0.92–1.03	0.32

* Based on chi-square testing.

** Based on logistic regression with generalized estimating equations to adjust standard errors for clustering within registry, also adjusting for all variables in the table.

*** Not reported due to confidentiality issues related to small sample sizes.

GnRH=gonadotropin-releasing hormone; SEER=Surveillance, Epidemiology, and End Results; Gleason grade 7 was categorized as moderately differentiated before January 1, 2003 and as poorly differentiated as of January 1, 2003.

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