

Risk of the “Androgen Deprivation Syndrome” in Men Receiving Androgen Deprivation for Prostate Cancer

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Background: Androgen deprivation therapy for prostate cancer has been associated with a spectrum of adverse effects, such as depression, memory difficulties, and fatigue, termed the *androgen deprivation syndrome*. Primary care physicians providing follow-up care for men with prostate cancer will be faced with managing these effects. We therefore sought to estimate the incidence of these effects and, by using a control group, ascertain whether these effects were related to androgen deprivation itself.

Methods: We assessed the risk of physician diagnoses of depression, cognitive impairment, or constitutional symptoms in Medicare data following androgen deprivation using a sample of 50 613 men with incident prostate cancer and 50 476 men without cancer, from 1992 through 1997, in the linked Surveillance, Epidemiology, and End Results–Medicare database. Cox proportional hazards regression was used to adjust for confounding variables.

Results: Of men surviving at least 5 years after diagnosis, 31.3% of those receiving androgen deprivation developed at least 1 depressive, cognitive, or constitutional diagnosis compared with 23.7% in those who did not ($P < .001$). After adjustment for variables such as comorbidity, tumor characteristics, and age, the risks associated with androgen deprivation were substantially reduced or abolished: relative risk (RR) for depression diagnosis, 1.08 (95% confidence interval [CI], 1.02–1.15); RR for cognitive impairment, 0.99 (95% CI, 0.94–1.04); and RR for constitutional symptoms, 1.17 (95% CI, 1.13–1.22).

Conclusion: Depressive, cognitive, and constitutional disorders occur more commonly in patients receiving androgen deprivation, but this appears to be primarily because patients receiving androgen deprivation are older and have more comorbid conditions and more advanced cancers.

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ANDROGEN DEPRIVATION HAS become a common treatment for prostate cancer, with nearly half of all men with the disease receiving the therapy at some point in their course of treatment.^{1,2} Androgen deprivation is increasingly used for early stages of prostate cancer, exposing men to the therapy for longer periods.^{2,3} In light of these trends, concerns about the toxic effects of androgen deprivation have been raised.^{4,5} Sexual dysfunction is a well-documented adverse effect of androgen deprivation.^{6–8} However, there is increasing recognition of a spectrum of other less specific adverse effects such as depression, anxiety, malaise, fatigue, and memory difficulties, which some authors have termed the *androgen deprivation syndrome*.^{9–16} The burden of managing these adverse effects will likely be faced by primary care physicians, who provide much of the long-term follow-up care for patients with prostate cancer.^{17,18} It is

therefore important to provide an estimate of the prevalence of these adverse effects. Previous studies examining these issues have been small, single center, and without controls.¹⁹ Because many of these effects could plausibly occur secondary to the cancer, controls are necessary to ascertain the impact of the androgen deprivation itself. We examined these adverse effects in a large, population-based sample using the linked Surveillance, Epidemiology and End-Results (SEER)–Medicare database.

METHODS

DATA SOURCES

Data used for this study derived from the linked SEER–Medicare database.^{20,21} The SEER program consists of a group of population-based tumor registries in selected geographic areas, from 11 states, covering approximately 14% of the US population. Medicare is a federal pro-

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Table 1. Definition of Disorders

Disorder*	Definition
Depressive	
Major depression	<i>ICD-9</i> diagnosis codes 296.2 and 296.3
Sleep disturbance related to depression	<i>ICD-9</i> diagnosis codes 307.41, 307.42, 307.43, 307.44
Depressive psychoses	<i>ICD-9</i> diagnosis codes 296.9 and 298.0
Depression with anxiety	<i>ICD-9</i> diagnosis codes 300.4
Adjustment disorder with depression	<i>ICD-9</i> diagnosis codes 309.0, 309.1, 309.28
Miscellaneous depressive disorders	<i>ICD-9</i> diagnosis codes 290.13, 290.21, 292.84, 296.5, 296.6, 296.7, 301.10, 301.12, 301.13, 311
Cognitive	
Senile dementia	<i>ICD-9</i> diagnosis codes 290.xx except 290.13 and 290.21
Organic or drug-related memory disturbances	<i>ICD-9</i> diagnosis codes 292.82, 292.83, 294, 310.1
Cerebral degenerations (eg, Alzheimer disease)	<i>ICD-9</i> diagnosis codes 331.xx
Constitutional	
Fatigue/malaise	<i>ICD-9</i> diagnosis code 780.79
Anorexia/cachexia/weight loss	<i>ICD-9</i> diagnosis codes 783.0, 783.1, 783.21, 783.22, 799.4
Abnormal weight gain	<i>ICD-9</i> diagnosis code 783.1
Debility	<i>ICD-9</i> diagnosis codes 300.5, 797, 799

Abbreviation: *ICD-9*, International Classification of Diseases, Ninth Revision.

*A disorder was deemed to occur if it was listed as a diagnosis in at least 1 claim in any of the outpatient, inpatient, or provider Medicare claims files.

gram that covers health services for 97% of persons 65 years and older. It provides data in the form of claims submitted by providers for reimbursement, which include information on diagnoses and the service, testing, or procedure carried out.

STUDY SUBJECTS

Prostate Cancer Cases

The study protocol was approved by the local institutional review board. All men 66 years and older first diagnosed as having prostate cancer in the years 1992 through 1997 were selected, for a total of 92 474 subjects. To ensure complete information, patients not enrolled in both Medicare Part A and Part B for the 12 months before and after their cancer diagnosis (13 352 cases), members of a health maintenance organization (17 275 cases), or those whose cancer was diagnosed by autopsy or on a death certificate (1076 cases) were excluded. Subjects with prostate cancer were divided into 2 groups: those who underwent androgen deprivation (defined as receipt of at least 1 dose of a gonadotropin-releasing hormone [GnRH] agonist or orchiectomy within 6 months of diagnosis) and those who did not receive androgen deprivation (defined as not receiving GnRH agonists or undergoing orchiectomy at any time following the diagnosis). This excluded 10 158 patients who started therapy with GnRH agonists or underwent orchiectomy 6 months or more after diagnosis. Overall, 50 613 patients with prostate cancer were available for the primary sample, with follow-up through 2001.

Noncancer Controls

As another comparison group, we developed a noncancer cohort from the SEER-Medicare data, which also includes a file containing a 5% sample of Medicare beneficiaries residing in the SEER areas who do not have any cancer diagnosis. We selected men 66 years and older who were resident in a SEER

area during the study period, had continuous Part A and Part B Medicare coverage, and were not enrolled in a health maintenance organization for at least 3 consecutive years between 1991 and 1997. The initial study entry year for these men was assigned randomly to match the distribution for the year of diagnosis of cancer in men in the prostate cancer cohort. In this way, we constructed a cohort of 50 476 men without cancer, with follow-up through 2001.

DEFINITIONS

Details for identification of variables of interest for this study such as patient demographic and socioeconomic characteristics, comorbid conditions, cancer treatments administered, and cancer characteristics have been previously published.⁸ Briefly, patient demographics such as age and race and tumor characteristics such as grade and American Joint Committee on Cancer (AJCC) stage were derived from the SEER Patient Entitlement and Diagnosis Summary file. Socioeconomic characteristics were based on ZIP code of residence through a linkage with the 1990 US census. Comorbidity was assessed using the modification of the Charlson comorbidity index²² by Klabunde et al,²³ based on information from Medicare inpatient and outpatient claims.²² Cancer treatments were also based on information from Medicare claims. Diagnoses that were potentially compatible with the androgen deprivation syndrome were grouped into 3 categories: depressive, cognitive, or constitutional disorders (Table 1). A disorder was deemed to occur if it was listed as a diagnosis at least once in a Medicare inpatient, outpatient, or physician claim.

STATISTICAL ANALYSIS

The χ^2 test was used to compare the proportions of patients with a diagnosis of a depressive, cognitive, or constitutional disorder in the 12 months prior to or during the 6- to 60-month period following the diagnosis of prostate cancer or study entry among patients with prostate cancer who received androgen deprivation, patients with prostate cancer who did not receive androgen deprivation, and patients without prostate cancer. To ensure complete follow-up for this analysis, patients who died or lost Medicare Part A or B coverage during the 60 months following diagnosis or study entry were excluded. In addition, patients who were diagnosed as having a disorder in the first 6 months of diagnosis of cancer or study entry were excluded because it was believed that these outcomes were less likely to be related to the androgen deprivation therapy.

Survival analyses were performed using Cox proportional hazards regression for patients with prostate cancer, with the dependent variable being time to first diagnosis of a disorder. Data were censored at death, end of follow-up period, or switch away from Medicare coverage. Patients who died or were diagnosed as having a disorder in the 6 months following diagnosis of cancer were excluded (inclusion of patients who developed disorders in the first 6 months following diagnosis did not substantially alter our results). The following characteristics were entered as independent variables in the model: use of androgen deprivation, age at diagnosis or study entry, race, education, income, SEER region, comorbidity, diagnosis of a depressive, cognitive or constitutional disorder in the 12 months prior to diagnosis or study entry, number of provider visits in the 12 months prior to diagnosis or study entry, cancer grade, cancer stage, use of radiation therapy, and use of radical prostatectomy. All analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). All tests of statistical significance were 2 sided, with $P < .05$ considered to be statistically significant.

RESULTS

PATIENT AND CANCER CHARACTERISTICS

Table 2 presents characteristics of the 50 613 men constituting the prostate cancer cohort, categorized by whether they received androgen deprivation (31% of the patients received androgen deprivation). Patients with prostate cancer who received androgen deprivation were older, with a median age of 75 years (vs 72 years), and 27.6% of patients were 80 years and older (vs 13.7%). Patients receiving androgen deprivation also tended to have more advanced and aggressive cancers, with 20.0% having AJCC stage IV tumors (vs 2.9%) and 33.9% having poorly differentiated tumors (vs 13.3%).

The characteristics of the 50 476 noncancer controls are also listed in Table 2. Their median age was 72 years. They tended to have slightly more comorbid conditions, with 7.5% of patients with a comorbidity index of 3 or higher vs 6.7% and 5.6% in the prostate cancer with androgen deprivation and without androgen deprivation groups, respectively.

PROPORTION OF PATIENTS WITH DEPRESSIVE, COGNITIVE, AND CONSTITUTIONAL DISORDERS

Depressive disorders during the 6- to 60-month period following diagnosis of cancer or study entry developed in a similar proportion of patients without cancer (9.6%; 95% confidence interval [CI], 9.2%-9.9%) and patients with prostate cancer who did not receive androgen deprivation (9.5%; 95% CI, 9.1%-9.9%) but were significantly more common in patients with prostate cancer receiving androgen deprivation (12.1%; 95% CI, 11.3%-12.8%) (**Table 3**). Cognitive disorders during the 6- to 60-month period following diagnosis or study entry were most common in the prostate cancer group who received androgen deprivation (13.9%; 95% CI, 13.1%-14.7%), intermediate in the prostate cancer group who did not receive androgen deprivation (10.2%; 95% CI, 9.8%-10.6%), and least common in the noncancer group (7.9%; 95% CI, 7.6%-8.2%). Constitutional disorders were most common in the prostate cancer group who received androgen deprivation (16.7%; 95% CI, 15.9%-17.6%), intermediate in the noncancer group (12.9%; 95% CI, 12.5%-13.3%), and least common in the prostate cancer group who did not receive androgen deprivation (11.4%; 95% CI, 10.9%-11.8%). The proportion of patients developing at least 1 depressive, cognitive, or constitutional disorder was 31.3% (95% CI, 30.2%-32.4%) in the prostate cancer group who received androgen deprivation, 23.7% (95% CI, 23.1%-24.3%) in the prostate cancer group who did not, and 22.9% (95% CI, 22.4%-23.4%) in the noncancer group.

RISK OF DEPRESSIVE, COGNITIVE, AND CONSTITUTIONAL DISORDERS ASSOCIATED WITH ANDROGEN DEPRIVATION THERAPY

A Cox model was performed to assess the risks of depressive, cognitive, and constitutional disorders associ-

Table 2. Patient and Cancer Characteristics*

Characteristic	Prostate Cancer Cases: Androgen Deprivation Therapy		Noncancer Controls
	Yes (n = 15 748)	No (n = 34 865)	(n = 50 476)
Age, y			
66-69	2753 (17.5)	9623 (27.6)	17 621 (34.9)
70-74	4503 (28.6)	12 661 (36.3)	14 191 (28.1)
75-79	4142 (26.3)	7792 (22.3)	9459 (18.7)
≥80	4350 (27.6)	4789 (13.7)	9205 (18.2)
Race			
White	13 100 (83.2)	29 430 (84.4)	42 249 (83.7)
Black	1485 (9.4)	3017 (8.7)	3017 (6.0)
Hispanic	257 (1.6)	508 (1.5)	1228 (2.4)
Other/unknown	906 (5.8)	1424 (4.1)	3982 (7.9)
ZIP code education, % adults with less than 12 years' education			
<12	3419 (23.0)	8352 (25.5)	9362 (23.4)
12 to <25	6796 (45.8)	14 872 (45.4)	18 500 (46.2)
25 to <35	2709 (18.3)	5798 (17.7)	7226 (18.0)
≥35	1910 (12.9)	3756 (11.5)	4975 (12.4)
Subtotal†	14 834	32 778	40 063
ZIP code poverty (median household income), \$			
<25 000	3181 (21.5)	7078 (21.7)	8512 (21.3)
25 000 to <35 000	4454 (30.1)	9974 (30.5)	12 329 (30.9)
35 000 to <45 000	3799 (25.7)	8548 (26.2)	10 354 (25.9)
≥45 000	3348 (22.6)	7076 (21.7)	8766 (21.9)
Subtotal†	14 782	32 676	39 961
Comorbidity index			
0	11 551 (73.3)	26 866 (77.1)	37 575 (74.4)
1	2371 (15.1)	4775 (13.7)	6770 (13.4)
2	772 (4.9)	1288 (3.7)	2322 (4.6)
≥3	1054 (6.7)	1936 (5.6)	3809 (7.5)
Grade			
Well-differentiated	1185 (7.5)	6506 (18.7)	
Moderately differentiated	7738 (49.1)	20 910 (60.0)	
Poorly differentiated/undifferentiated	5343 (33.9)	4651 (13.3)	
Unknown	1482 (9.4)	2798 (8.0)	
AJCC stage			
I	96 (0.6)	1397 (4.0)	
II	4779 (30.3)	12 672 (36.3)	
III	1548 (9.8)	4922 (14.1)	
IV	3152 (20.0)	1002 (2.9)	
Unknown	6173 (39.2)	14 872 (42.7)	
Radical prostatectomy			
No	14 102 (89.5)	24 782 (71.1)	
Yes	1646 (10.5)	10 083 (28.9)	
Radiation			
No	11 297 (71.7)	21 000 (60.2)	
Yes	4451 (28.3)	13 865 (39.8)	

Abbreviation: AJCC, American Joint Committee on Cancer.

*Data are given as number (percentage) of patients unless otherwise specified.

†Missing data.

ated with androgen deprivation therapy. The analysis was limited to patients with prostate cancer, and the aim was to compare the risk of disorders between patients who received androgen deprivation with those who did not. Subjects were followed for a mean of 52 months following diagnosis of cancer.

Table 3. Proportion of Patients With Disorders in the 12 Months Before vs 6 to 60 Months After Diagnosis or Study Entry

Disorder/Cancer Status	Androgen Deprivation (No.)*	Patients With a Disorder in the 12 mo Before Diagnosis		Patients With a Disorder 6-60 mo After Diagnosis			
		%	P Value	%	P Value	P Value	P Value
Depressive Disorders							
Major depression							
Prostate cancer	Yes (6883)	0.35		3.39	.002	.73	.003
Noncancer	No (20416)	0.37	.92	2.66			
	No (26513)	0.35		2.71			
Sleep disturbance related to depression							
Prostate cancer	Yes (6883)	0.04		0.29	.10	.55	.22
Noncancer	No (20416)	0.01	.17	0.19			
	No (26513)	0.03		0.21			
Depression with psychosis							
Prostate cancer	Yes (6883)	0.03		0.22	.209	.08	.99
Noncancer	No (20416)	0.02	.87	0.15			
	No (26513)	0.02		0.22			
Depression with anxiety							
Prostate cancer	Yes (6883)	0.28		1.90	.29	.87	.23
Noncancer	No (20416)	0.32	.83	1.71			
	No (26513)	0.32		1.69			
Adjustment disorder with depression							
Prostate cancer	Yes (6883)	0.25		2.03	.07	.99	.06
Noncancer	No (20416)	0.22	.13	1.69			
	No (26513)	0.15		1.69			
Miscellaneous depressive disorders							
Prostate cancer	Yes (6883)	0.97		8.44	<.001	.51	<.001
Noncancer	No (20416)	0.60	.002	6.13			
	No (26513)	0.83		6.28			
Any depressive disorder							
Prostate cancer	Yes (6883)	1.73		12.07	<.001	.75	<.001
Noncancer	No (20416)	1.41	.16	9.46			
	No (26513)	1.47		9.55			
Cognitive Disorders							
Senile dementia							
Prostate cancer	Yes (6940)	0.35		5.99	<.001	<.001	.02
Noncancer	No (20561)	0.18		4.31			
	No (26795)	0.40	<.001	5.26			
Organic or drug-related memory disturbance							
Prostate cancer	Yes (6940)	0.22		5.63	<.001	<.001	<.001
Noncancer	No (20561)	0.18	.65	4.36			
	No (26795)	0.16		3.16			
Cerebral degenerations							
Prostate cancer	Yes (6940)	0.66		9.37	<.001	<.001	<.001
Noncancer	No (20561)	0.66		6.83			
	No (26795)	0.18	<.001	2.80			
Any cognitive disorder							
Prostate cancer	Yes (6940)	1.14		13.88	<.001	<.001	<.001
Noncancer	No (20561)	0.95		10.23			
	No (26795)	0.68	<.001	7.91			

(continued)

Unadjusted analyses demonstrated significant increases in the risk of depressive (relative risk [RR], 1.37; 95% CI, 1.30-1.44), cognitive (RR, 1.44; 95% CI, 1.38-1.50), and constitutional (RR, 1.57; 95% CI, 1.51-1.62) disorders associated with receipt of androgen deprivation. In adjusted analyses, these risks were substantially reduced or eliminated. The RR was 1.08 (95% CI, 1.02-1.15) for depressive disorders, 0.99 (95% CI, 0.94-1.04) for cognitive disorders, and 1.17 (95% CI, 1.13-1.22) for constitutional disorders.

We performed a series of additional analyses. First, to examine whether the effect of androgen deprivation differed in healthier patients with earlier-stage cancers, we restricted the analyses to patients with early stage disease (AJCC stage I or II and low- or moderate-grade histologic features), age younger than 80 years at diagnosis, and a comorbidity index of 0. The pattern was similar to the results for the analyses that included all patients. For depressive disorders, the unadjusted risk associated with androgen deprivation was 1.28 (95% CI, 1.12-

Table 3. Proportion of Patients With Disorders in the 12 Months Before vs 6 to 60 Months After Diagnosis or Study Entry (cont)

Disorder/Cancer Status	Androgen Deprivation (No.)*	Patients With a Disorder in the 12 mo Before Diagnosis		Patients With a Disorder 6-60 mo After Diagnosis		
		%†	P Value	%†	P Value (‡ vs §)	P Value (§ vs)
Constitutional Disorders						
Fatigue/malaise						
Prostate cancer	Yes (7001)	0.00		11.27	<.001	<.001
	No (20701)	0.00		7.60		
Noncancer	No (26911)	0.00		9.07		
Anorexia/cachexia/weight loss						
Prostate cancer	Yes (7001)	0.26		2.61	<.001	.16
	No (20701)	0.18		1.73		
Noncancer	No (26911)	0.18		1.91		
Abnormal weight gain						
Prostate cancer	Yes (7001)	0.07		1.36	<.001	.31
	No (20701)	0.12		0.79		
Noncancer	No (26911)	0.11		0.87		
Debility						
Prostate cancer	Yes (7001)	0.27		3.30	<.001	.87
	No (20701)	0.18		2.33		
Noncancer	No (26911)	0.21		2.35		
Any constitutional disorder						
Prostate cancer	Yes (7001)	0.60		16.74	<.001	<.001
	No (20701)	0.48		11.36		
Noncancer	No (26911)	0.50		12.91		

Abbreviation: ND, not done.

*Including only patients who survived to 60 months following diagnosis and had continuous Medicare Part A and B coverage for the entire period, excluding patients who developed disorders within 6 months following diagnosis or study entry.

†Calculated as the fraction of patients who developed at least 1 occurrence of a disorder during the period of interest (12 months before diagnosis or 6-60 months following study entry or the diagnosis of cancer).

‡Patients with prostate cancer who received androgen deprivation.

§Patients with prostate cancer who did not receive androgen deprivation.

||Noncancer patients.

1.47), and this fell to 1.19 (95% CI, 1.03-1.37) in the adjusted analysis. For cognitive disorders, the unadjusted risk associated with androgen deprivation was 1.29 (95% CI, 1.13-1.46), and this fell to 1.10 (95% CI, 0.96-1.26) in the adjusted analysis. For constitutional disorders, the unadjusted risk associated with androgen deprivation was 1.62 (95% CI, 1.49-1.77), and this fell to 1.22 (95% CI, 1.11-1.34) in the adjusted analysis.

Second, to examine whether the effects differed in patients receiving prolonged androgen deprivation, we analyzed the risks for depressive, cognitive, and constitutional disorders associated with use of at least 9 doses of a GnRH agonist in the first year and the risks associated with orchiectomy performed in the first 6 months of diagnosis. For orchiectomy, there was a slightly higher risk for depressive disorders (RR, 1.15; 95% CI, 1.03-1.27). Otherwise, the results were essentially unchanged from the analyses for overall androgen deprivation.

Third, we performed another Cox model including both patients with and without prostate cancer. This analysis included adjustment for the same variables included in the previous Cox models except for the cancer-related variables. Patients without cancer were the reference group. For patients with prostate cancer receiving androgen deprivation compared with patients without cancer, the RR was 1.13 (95% CI, 1.08-1.19) for depressive disorders and 1.26 (95% CI, 1.21-1.30) for constitutional disorders. There were no significant differ-

ences in the risks of depressive or constitutional disorders between patients with prostate cancer who did not receive androgen deprivation vs the noncancer controls. The risk of cognitive disorders was significantly increased in patients with prostate cancer with and without androgen deprivation compared with the noncancer group, with RRs of 1.32 (95% CI, 1.27-1.38) and 1.20 (95% CI, 1.15-1.24), respectively.

COMMENT

To our knowledge, this study is the first population-based analysis of depressive, cognitive, and constitutional diagnoses in patients with prostate cancer receiving androgen deprivation. In unadjusted analyses, the risks of depressive, cognitive, and constitutional disorders were substantially increased in patients receiving androgen deprivation. However, after adjustment for potentially confounding variables such as tumor grade and comorbidity, the risks declined substantially. There were still small but significant increases in the risks of depressive and constitutional disorders in patients with prostate cancer who received androgen deprivation compared with those who did not.

Potential complications of androgen deprivation have received increasing attention because of recent trends in the use of this therapy. Despite no demonstrated survival

benefit, androgen deprivation therapy is now commonly used for early primary treatment of localized and locally advanced disease, as well as for biochemical recurrence following radical prostatectomy.² In addition, there has been a dramatic rise in its use as adjuvant therapy combined with radiation in locally advanced or high-risk subsets of localized disease in the face of clinical trials showing improved survival with this regimen.^{3,24,25} These changes have led to more men with prostate cancer being exposed to androgen deprivation and for longer periods.

There are good theoretical reasons to suspect that androgen deprivation may cause the emotional disturbances, fatigue, and memory difficulties that have collectively been termed the *androgen deprivation syndrome*. Although data are conflicting, some studies of elderly men have demonstrated an association between low testosterone levels and depressive illness.^{26,27} Furthermore, a study of 4 hypogonadal men with depression refractory to conventional therapy showed dramatic improvement following testosterone replacement, with relapses occurring in 3 after switching to placebo.²⁸ Low testosterone levels are also associated with poorer cognitive function.²⁹ A controlled trial of testosterone administration in 25 healthy older men showed improvements in spatial and verbal memory.³⁰ Finally, fatigue could plausibly result from reductions in muscle mass that occur following androgen deprivation.^{31,32}

Despite biological plausibility, studies specifically addressing the association between androgen deprivation in prostate cancer and subsequent depressive, cognitive, or constitutional symptoms are limited. Previous reports examining the risk of depression in patients with prostate cancer receiving androgen deprivation are restricted to case series or small cohort studies without a control group.^{10,12,13} The largest study, involving 45 men receiving androgen deprivation, demonstrated a prevalence of major depression of 12.8%, which the authors noted to be 8 times the national rate of depression in men.¹³ Results from studies examining the effect of androgen deprivation on cognitive function in patients with prostate cancer are conflicting.^{14,33} A clinical trial assessed cognitive function in 82 men with prostate cancer randomized to active treatment with androgen deprivation vs observation alone.¹⁴ Nearly 50% of the men in the treatment arm developed a decline in the results of 1 or more cognitive tests after 6 months of therapy, whereas no declines were noted in the observation group. In contrast, an observational study of 25 men receiving androgen deprivation together with radiation showed no decline in cognitive function after 12 months of therapy.³³ Finally, only 1 uncontrolled study specifically examined fatigue in the setting of androgen deprivation for prostate cancer.¹⁵ A total of 62 men with prostate cancer were assessed using a fatigue questionnaire at baseline and after 3 months of therapy with a GnRH agonist, and 66% described a worsening in their fatigue score after therapy was initiated.

Recent reviews on complications of androgen deprivation in patients with prostate cancer note that effects such as depression and fatigue can and have been attributed to the cancer itself or to other medical comorbid conditions.^{7,19} In this regard, cancers of various sites have

been associated with depression, fatigue, and cognitive dysfunction, with worse symptoms in patients with more advanced cancers.^{34,35} Similar associations have been described with chronic medical illness in the elderly.^{36,37} Evidence from our study shows that although depressive, cognitive, and constitutional disorders occur more commonly in patients receiving androgen deprivation, this is primarily because patients receiving androgen deprivation are older, have more comorbid conditions, and have more advanced cancers (Table 2).² These disorders therefore may not be causally related to the androgen deprivation itself. After adjustment, the risks of these disorders were substantially reduced or abolished. This remained true even when we limited the analyses to the risks associated with prolonged androgen deprivation in the form of orchectomy. The small residual increases in risk of depressive or constitutional disorders in adjusted analyses may represent true but modest effects of androgen deprivation or may plausibly be due to incomplete adjustment and residual confounding.

The main limitation of this study is the issue of ascertainment of the disorders. A Medicare claims approach is known to have poor sensitivity for diagnoses not associated with a procedure.³⁸ In addition, patients often do not report symptoms such as fatigue or depression to their physicians.³⁹ As such, rates of the disorders noted in Table 3 probably represent underestimates of the true prevalence of these conditions. However, because the method of ascertainment of the disorders was similar among all the groups studied, the RRs generated should still be valid. In addition, the large sample size in our study allowed relatively precise estimates of the risks, making it unlikely that a large effect of androgen deprivation was missed because of insufficient power. Nevertheless, we cannot exclude the presence of subtle effects of androgen deprivation that require formal cognitive or psychological testing to detect.

There are a number of implications from this study. The presence of substantial confounding in the assessment of the effect of androgen deprivation on the occurrence of depressive, cognitive, and constitutional disorders underscores the need for controls in all future studies examining these issues. The risks of depression or constitutional effects directly attributable to androgen deprivation are at best modest and should not preclude the use of this therapy in settings in which its benefits are clear. Nevertheless, these conditions are especially common in patients with prostate cancer receiving androgen deprivation, affecting at least 30% of men over a 5-year period. Primary care physicians and urologists treating these patients should therefore be aware of the potential for these disorders to develop and encourage patients to report relevant symptoms. Effective treatments are available for some of these conditions and may help improve the quality of life for patients with prostate cancer.

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