

ORIGINAL ARTICLE

## Risk of Fracture after Androgen Deprivation for Prostate Cancer

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ABSTRACT

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### BACKGROUND

The use of androgen-deprivation therapy for prostate cancer has increased substantially over the past 15 years. This treatment is associated with a loss of bone-mineral density, but the risk of fracture after androgen-deprivation therapy has not been well studied.

### METHODS

We studied the records of 50,613 men who were listed in the linked database of the Surveillance, Epidemiology, and End Results program and Medicare as having received a diagnosis of prostate cancer in the period from 1992 through 1997. The primary outcomes were the occurrence of any fracture and the occurrence of a fracture resulting in hospitalization. Cox proportional-hazards analyses were adjusted for characteristics of the patients and the cancer, other cancer treatment received, and the occurrence of a fracture or the diagnosis of osteoporosis during the 12 months preceding the diagnosis of cancer.

### RESULTS

Of men surviving at least five years after diagnosis, 19.4 percent of those who received androgen-deprivation therapy had a fracture, as compared with 12.6 percent of those not receiving androgen-deprivation therapy ( $P < 0.001$ ). In the Cox proportional-hazards analyses, adjusted for characteristics of the patient and the tumor, there was a statistically significant relation between the number of doses of gonadotropin-releasing hormone received during the 12 months after diagnosis and the subsequent risk of fracture.

### CONCLUSIONS

Androgen-deprivation therapy for prostate cancer increases the risk of fracture.

**A**NDROGEN-DEPRIVATION THERAPY FOR prostate cancer can reduce morbidity, palliate metastases, and improve survival in locally advanced disease when combined with radiation.<sup>1-3</sup> However, androgen-deprivation therapy alone, in the form of gonadotropin-releasing hormone agonists, is increasingly being used in men with localized prostate cancer (cancer confined to the prostate) and in men in whom the level of prostate-specific antigen (PSA) rises after prostatectomy<sup>4-6</sup> — both situations in which most patients are minimally symptomatic and no survival benefit has been demonstrated.<sup>1,7</sup> For these reasons, it is important to have accurate data on the toxic effects of androgen deprivation.<sup>8,9</sup> Bone fractures are of particular concern, given their association with increased mortality in prostate cancer.<sup>10</sup>

A rapid loss of bone-mineral density occurs within the first 6 to 12 months of androgen-deprivation therapy.<sup>11,12</sup> However, the assessment of the risk of fracture associated with this treatment has been limited in previous studies by small numbers and the lack of a control group.<sup>13-16</sup> We used the linked database of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and Medicare to assess the risk of fracture associated with androgen deprivation in the form of orchiectomy or treatment with gonadotropin-releasing hormone agonists in a large population-based sample of men who received the diagnosis of prostate cancer during the period from 1992 through 1997.

## METHODS

The study protocol was approved by the local institutional review board; because of the study design, the requirement of informed consent was waived.

### DATA SOURCES

The SEER-Medicare database links two large population-based sources of data that together provide information on older adults with newly diagnosed cancer.<sup>17</sup> During the 1990s, the SEER program consisted of a group of 11 tumor registries that represented approximately 14 percent of the population.

### STUDY SUBJECTS

Data on all men 66 years of age or older who received a first diagnosis of prostate cancer in the years from 1992 through 1997 were selected, for a total of 92,474 subjects. To ensure complete infor-

mation, we excluded patients who were not enrolled in both Part A and Part B Medicare for the 12 months before the diagnosis and the 12 months after the diagnosis (13,352 cases), were members of a health maintenance organization (17,275 cases), or whose disease had been diagnosed on autopsy or on a death certificate (1076 cases). We limited the comparisons to men with prostate cancer who received at least one dose of a gonadotropin-releasing hormone agonist or underwent orchiectomy within six months after receiving the diagnosis with those with prostate cancer who received neither type of treatment at any time after diagnosis. This limitation excluded 10,158 patients who had started treatment with gonadotropin-releasing hormone agonists or had undergone orchiectomy six months or more after diagnosis. We also performed an analysis that included all patients who received androgen-deprivation therapy during the first 24 months after diagnosis, and this analysis did not substantially alter our results. Overall, data were available for a total of 50,613 patients for the primary sample, with follow-up through 2001.

The variables used in this study are defined in the Supplementary Appendix, which is available with the full text of this article at [www.nejm.org](http://www.nejm.org).<sup>18-28</sup> The primary outcomes were any fracture and fracture resulting in hospitalization. Secondary outcomes were a new diagnosis of osteoporosis and fractures at specific sites.

### STATISTICAL ANALYSIS

The chi-square test was used to compare the proportions of patients who were treated with androgen deprivation according to different categories of baseline characteristics and to compare the proportions of patients with bone-related toxic effects according to the presence or absence of androgen-deprivation therapy. The Kaplan-Meier method was used to generate estimates of unadjusted, fracture-free survival. Survival analyses were performed with the use of Cox proportional-hazards regression. The dependent variable was either the time to a first fracture or the time to a first fracture that resulted in hospitalization, depending on the outcome being analyzed. Patients were censored at death, the loss of coverage under Medicare Part A or Part B, or a change to coverage under a health maintenance organization. An examination for interaction between prespecified variables of interest (age, cancer stage, race, and score on a modified form of the Charlson comorbidity index<sup>18,19</sup>) and the presence

Table 1. Characteristics of the Patients.\*

Characteristic	All Patients	Patients Who Received Androgen-Deprivation Therapy†	P Value‡
	no.	%	
Total	50,613	31.1	
Age			
66–69 yr	12,376	22.2	<0.001
70–74 yr	17,164	26.2	
75–79 yr	11,934	34.7	
≥80 yr	9,139	47.6	
Race or ethnic group§			
White	41,147	30.6	<0.001
Black	4,776	29.8	
White Hispanic	1,941	35.3	
Other or unknown	2,749	38.7	
SEER region			
San Francisco	3,777	31.1	<0.001
Connecticut	6,425	35.9	
Michigan	9,420	27.3	
Hawaii	1,309	35.2	
Iowa	6,458	34.7	
New Mexico	2,495	19.7	
Seattle	5,468	25.0	
Utah	2,903	25.1	
Georgia	3,144	27.4	
San Jose, Calif.	1,962	38.2	
Los Angeles	7,252	38.6	
Grade of prostate cancer			
Well differentiated	7,691	15.4	<0.001
Moderately differentiated	28,648	27.0	
Poorly differentiated or undifferentiated	9,994	53.5	
Unknown	4,280	34.6	
AJCC stage			
I (incidental finding)	1,493	6.4	<0.001
II (localized to prostate)	17,451	27.4	
III (locally advanced)	6,470	23.9	
IV (distant spread)	4,154	75.9	
Unknown	21,045	29.3	

or absence of androgen-deprivation therapy on the relative risk of fracture was performed with the use of a Cox model. Race was determined on the basis of the codes for racial and ethnic groups used in the SEER database.

The numbers needed to harm were calculated by taking the inverse of the difference between the

rates of fracture adjusted in the Cox model at five years after diagnosis for the group that did not receive androgen-deprivation therapy and the group that did receive it. Although numbers needed to harm are usually reserved for the analysis of clinical trials, we use them here to provide a measure of the absolute effect of androgen-deprivation thera-

**Table 1. (Continued.)**

Characteristic	All Patients	Patients Who Received Androgen-Deprivation Therapy†	P Value‡
	no.	%	
Year of diagnosis			
1992	11,412	26.5	<0.001
1993	9,474	26.7	
1994	7,880	29.4	
1995	7,343	31.9	
1996	7,117	36.4	
1997	7,387	40.0	
<12 Yr of education¶			
<10%	11,594	29.3	<0.001
10–<20%	17,200	31.0	
20–<30%	11,971	31.9	
≥30%	8,955	32.5	
Income below poverty line¶			
<3%	9,628	30.4	0.45
3 to <7%	15,503	31.2	
7 to <14%	13,746	31.3	
≥14%	10,843	31.3	
Modified Charlson comorbidity index <sup>18,19</sup>			
0	38,417	30.1	<0.001
1	7,146	33.2	
2	2,060	37.5	
≥3	2,990	35.3	
Other treatment within 6 mo after diagnosis			
Radical prostatectomy	10,884	13.6	<0.001
Radiation	17,471	24.5	
Both	845	19.4	
Neither	21,413	45.8	

\* SEER denotes Surveillance, Epidemiology, and End Results Program, and AJCC American Joint Committee on Cancer.

† Androgen-deprivation therapy consisted of at least one dose of a gonadotropin-releasing hormone agonist within six months after the diagnosis of prostate cancer.

‡ P values were derived with the chi-square test.

§ Race or ethnic group was determined on the basis of the codes for race and ethnic group used in the SEER database.

¶ Census-tract data were missing for 893 subjects.

py on the risk of fracture. All analyses were performed with the use of SAS software (version 8.2) (SAS Institute).

## RESULTS

### PROPORTION OF PATIENTS RECEIVING STUDY TREATMENT

Table 1 presents the percentages of 50,613 men 66 years of age or older with prostate cancer who

received androgen-deprivation therapy (in the form of either gonadotropin-releasing hormone agonists or orchiectomy) within six months after diagnosis as a function of the characteristics of the patients and the cancer. The rate of use of androgen-deprivation treatment increased with increasing age, the stage of the cancer at diagnosis, the grade of prostate cancer, and the presence of coexisting conditions. In addition, there was an increase in the use of androgen-deprivation therapy over the period from

**Table 2. Proportions of Patients with Bone-Related Toxic Effects before and after the Diagnosis of Prostate Cancer, According to the Presence or Absence of Androgen-Deprivation Therapy.\***

Toxic Effect	12 Mo before Diagnosis	P Value	12 to 60 Mo after Diagnosis	P Value
	%		%	
Osteoporosis		0.19		<0.001
Androgen-deprivation therapy	0.59		6.92	
No androgen-deprivation therapy	0.46		3.69	
Any fracture		0.01		<0.001
Androgen-deprivation therapy	3.41		19.37	
No androgen-deprivation therapy	2.80		12.63	
Fracture resulting in hospitalization		0.49		<0.001
Androgen-deprivation therapy	0.26		5.19	
No androgen-deprivation therapy	0.21		2.37	
Fracture site				
Skull		0.70		0.006
Androgen-deprivation therapy	0.18		1.23	
No androgen-deprivation therapy	0.20		0.86	
Spine		0.44		<0.001
Androgen-deprivation therapy	0.36		3.20	
No androgen-deprivation therapy	0.30		1.64	
Rib		0.02		<0.001
Androgen-deprivation therapy	0.63		3.77	
No androgen-deprivation therapy	0.40		2.44	
Pelvis		0.53		0.002
Androgen-deprivation therapy	0.06		1.07	
No androgen-deprivation therapy	0.08		0.68	
Upper arm		0.62		<0.001
Androgen-deprivation therapy	0.30		2.21	
No androgen-deprivation therapy	0.26		1.19	
Lower arm		0.89		<0.001
Androgen-deprivation therapy	0.21		2.08	
No androgen-deprivation therapy	0.22		1.04	
Hand		0.79		<0.001
Androgen-deprivation therapy	0.57		3.16	
No androgen-deprivation therapy	0.54		1.99	
Femoral neck (hip)		0.02		<0.001
Androgen-deprivation therapy	0.44		4.06	
No androgen-deprivation therapy	0.26		2.06	
Other parts of femur		0.47		<0.001
Androgen-deprivation therapy	0.06		1.17	
No androgen-deprivation therapy	0.09		0.64	
Lower leg		0.36		<0.001
Androgen-deprivation therapy	0.36		2.24	
No androgen-deprivation therapy	0.29		1.56	
Foot		0.28		<0.001
Androgen-deprivation therapy	0.44		2.17	
No androgen-deprivation therapy	0.34		1.48	

\* Only patients who survived to 60 months after diagnosis and had continuous coverage under Medicare Parts A and B for the entire period were included. Patients who had bone-related outcomes within the 12 months after diagnosis were excluded. The proportion was calculated as the fraction of patients in whom at least one bone-related toxic effect developed during the relevant period. P values are for the comparison between androgen-deprivation therapy and no androgen-deprivation therapy. For the analysis of toxic effects, there were 6650 patients who received androgen-deprivation therapy and 20,035 who did not, with the exception of the analysis of osteoporosis, in which there were 6953 patients who received androgen-deprivation therapy and 20,614 who did not.

1992 to 1997, and the lowest to the highest rates of use among the SEER geographic regions differed by a factor of two.

#### PROPORTION OF PATIENTS WITH BONE-RELATED TOXIC EFFECTS

The rates of occurrence of various bone-related toxic effects during the 12 months before the diagnosis of prostate cancer and during the period of 12 to 60 months after diagnosis were compared between the group that received androgen-deprivation therapy and the group that did not (Table 2). To ensure complete follow-up, data on patients who died or lost coverage under Medicare Part A or Part B during the 60 months after diagnosis were excluded. In addition, data on patients with bone-related toxic effects that occurred during the first 12 months after diagnosis were excluded, because these outcomes were considered unlikely to be related to the therapy (and reanalysis including these patients did not substantially alter the results).

There was a small but statistically significant increase in the proportion of patients with any fracture during the 12 months before diagnosis in the group that received androgen-deprivation therapy as compared with the group that did not receive androgen-deprivation therapy. All bone-related toxic effects developed significantly more frequently during the 12 to 60 months after diagnosis in the androgen-deprivation group. During this period, 19.4 percent of those in the androgen-deprivation group had a fracture, as compared with 12.6 percent of those not receiving the study treatment ( $P < 0.001$ ). In the same four-year period, 5.2 percent of those treated with androgen-deprivation therapy were hospitalized with a fracture, as compared with 2.4 percent of those not treated ( $P < 0.001$ ).

We repeated the analysis shown in Table 2, restricting it to data on patients with stage I, II, or III disease according to the criteria of the American Joint Committee on Cancer (AJCC) and low-grade or moderate-grade prostate cancer. The results of the two analyses were similar. For example, the rate of hospitalization with fracture in the latter analysis was 4.9 percent among patients who received androgen-deprivation therapy as compared with 2.2 percent among those who did not ( $P < 0.001$ ).

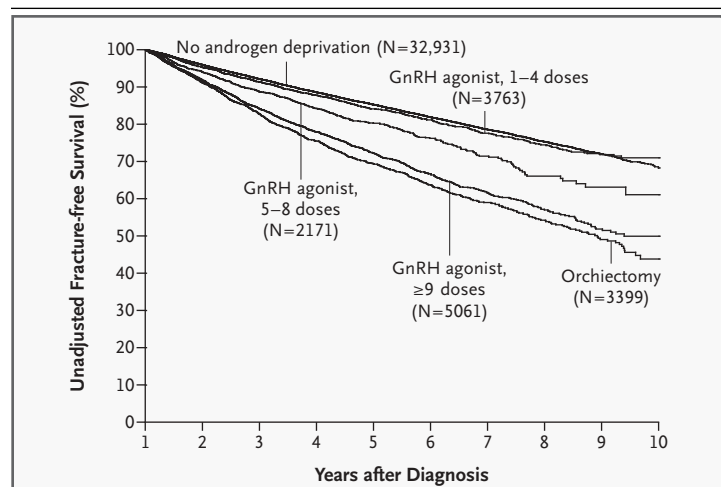
#### UNADJUSTED FRACTURE-FREE SURVIVAL

The Kaplan–Meier method was used to generate unadjusted estimates of survival free of any fracture among the groups that did or did not receive

androgen-deprivation therapy (Fig. 1). All subjects who survived at least 12 months after the diagnosis of prostate cancer were included in the analysis. Androgen-deprivation therapy was divided between those who underwent orchiectomy and those who received gonadotropin-releasing hormone agonists, stratified according to the number of doses received (one to four, five to eight, or nine or more doses) in the year after diagnosis. Patients who had fractures in the first year after diagnosis were excluded. Those who underwent orchiectomy and those who received nine or more doses of gonadotropin-releasing hormone agonists in the year after diagnosis had the lowest rates of fracture-free survival. The curves for the groups that underwent orchiectomy or received five to eight doses or nine or more doses of gonadotropin-releasing hormone agonists diverged from that for the group that did not receive androgen-deprivation therapy over the entire period of follow-up.

#### FRACTURE RISK AND ANDROGEN-DEPRIVATION THERAPY

The risk of any fracture associated with androgen-deprivation therapy was assessed with the use of a Cox regression model adjusted for variables related to the patient and the cancer, other cancer treatment received, and a diagnosis of fracture, os-



**Figure 1. Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy.**

The survival curves start at 12 months after diagnosis, and androgen deprivation was initiated within 6 months after diagnosis. GnRH denotes gonadotropin-releasing hormone. The number of doses is the number administered within 12 months after diagnosis.

teoporosis, or osteopenia during the year before the diagnosis of cancer (Table 3). Patients who died during the year after diagnosis or who had fractures during those 12 months were excluded. Subjects were followed for a mean of 5.1 years after diagnosis.

The relative risk of the occurrence of any fracture or a fracture that resulted in hospitalization increased steadily with the increasing number of doses of a gonadotropin-releasing hormone agonist received during the first year after diagnosis ( $P < 0.001$  for linear trend). This trend was also significant ( $P < 0.001$ ) when the number of doses of a gonadotropin-releasing hormone agonist received during the 24 months after diagnosis was examined (data not shown). The relative risk of any fracture was 1.45 (95 percent confidence interval, 1.36

to 1.56) among those receiving nine or more doses of gonadotropin-releasing hormone agonist in the first 12 months after diagnosis and 1.54 (95 percent confidence interval, 1.42 to 1.68) among those who underwent orchiectomy. For the relative risk of fracture resulting in hospitalization, the risk was 1.66 (95 percent confidence interval, 1.47 to 1.87) for nine or more doses of gonadotropin-releasing hormone agonist and 1.70 (95 percent confidence interval, 1.48 to 1.96) for orchiectomy.

With reference to the sites of fracture typically associated with osteoporosis (e.g., hip, spine, and forearm), the relative risk was 1.62 (95 percent confidence interval, 1.47 to 1.78) for nine or more doses of gonadotropin-releasing hormone agonist in the year after diagnosis and 1.63 (95 percent confidence interval, 1.45 to 1.82) for orchiectomy. Among

**Table 3. Risk of Fracture Associated with Androgen-Deprivation Therapy.\***

Variable	Any Fracture†	Fracture Resulting in Hospitalization†
	RR (95% CI)	RR (95% CI)
Androgen-deprivation therapy		
None	1.00	1.00
Gonadotropin-releasing hormone agonist‡		
1–4 doses	1.07 (0.98–1.16)	0.98 (0.82–1.17)
5–8 doses	1.22 (1.11–1.35)	1.51 (1.26–1.80)
≥9 doses	1.45 (1.36–1.56)	1.66 (1.47–1.87)
Orchiectomy	1.54 (1.42–1.68)	1.70 (1.48–1.96)
Age (in 5-yr categories)	1.21 (1.19–1.24)	1.45 (1.40–1.50)
Race or ethnic group		
White	1.00	1.00
Black	0.79 (0.72–0.86)	0.63 (0.52–0.77)
White Hispanic	0.88 (0.78–1.00)	0.76 (0.60–0.96)
Other or unknown	0.78 (0.69–0.87)	0.62 (0.50–0.77)
Grade of prostate cancer		
Well differentiated	1.00	1.00
Moderately differentiated	1.05 (0.98–1.12)	1.03 (0.90–1.17)
Poorly differentiated or undifferentiated	1.14 (1.05–1.24)	1.18 (1.02–1.37)
Unknown	1.08 (0.98–1.18)	1.10 (0.93–1.30)
AJCC stage		
I	1.00	1.00
II	1.03 (0.90–1.18)	1.05 (0.81–1.35)
III	1.12 (0.96–1.29)	1.12 (0.84–1.48)
IV	1.29 (1.11–1.51)	1.42 (1.07–1.88)
Unknown	1.08 (0.95–1.24)	1.10 (0.86–1.40)

patients with nonmetastatic disease (AJCC stage I, II, or III and a low-to-moderate grade of prostate cancer), the relative risk of any fracture was 1.37 (95 percent confidence interval, 1.20 to 1.57) for nine or more doses of gonadotropin-releasing hormone agonist. In the analyses limited to patients who received androgen deprivation as primary therapy (with patients who underwent radical prostatectomy or radiation excluded) or to patients who received androgen deprivation as adjuvant therapy (concomitantly with radical prostatectomy or radiation), the relative risks of any fracture were 1.44 (95 percent confidence interval, 1.33 to 1.56) and 1.53 (95 percent confidence interval, 1.32 to 1.78), respectively, among those receiving nine or more doses of gonadotropin-releasing hormone agonist.

#### EXAMINATION FOR INTERACTION

Interactions were tested on the basis of the Cox model presented in Table 3. There were no statistically significant interactions between cancer stage or race or ethnic group and androgen deprivation. There were significant interactions between scores on the comorbidity index and androgen deprivation ( $P=0.005$ ), and between age and androgen deprivation ( $P=0.01$ ) on the risk of fracture. The relative risk of any fracture at different doses of gonadotropin-releasing hormone agonist or with orchiectomy tended to decline with advancing age, although subjects 80 years of age or older who received nine or more doses of gonadotropin-releasing hormone agonist were still at an increased risk of subsequent fracture (relative risk, 1.32; 95 percent confidence

**Table 3. (Continued.)**

Variable	Any Fracture <sup>†</sup> RR (95% CI)	Fracture Resulting in Hospitalization <sup>†</sup> RR (95% CI)
Year of diagnosis		
1992	1.00	1.00
1993	0.99 (0.93–1.05)	1.02 (0.91–1.14)
1994	0.99 (0.93–1.06)	1.03 (0.91–1.17)
1995	1.05 (0.98–1.12)	0.97 (0.84–1.11)
1996	0.99 (0.92–1.07)	0.97 (0.83–1.12)
1997	0.94 (0.86–1.01)	1.01 (0.86–1.18)
Comorbidity index		
0	1.00	1.00
1	1.15 (1.09–1.22)	1.23 (1.10–1.38)
2	1.11 (0.99–1.23)	1.24 (1.03–1.49)
≥3	1.27 (1.16–1.39)	1.56 (1.33–1.83)
Radical prostatectomy	0.73 (0.68–0.78)	0.50 (0.43–0.59)
Radiation	0.89 (0.84–0.93)	0.79 (0.71–0.88)

\* RR denotes relative risk, and AJCC American Joint Committee on Cancer.

<sup>†</sup> Patients who had fractures or who died during the first 12 months after diagnosis were excluded. All patients had to have continuous coverage under Medicare Parts A and B for at least 12 months before and after diagnosis. Cox proportional-hazards regression was performed with the time to fracture as the dependent variable and the following entered simultaneously as dependent variables: the presence or absence of androgen-deprivation therapy, age, race or ethnic group, SEER region, grade of prostate cancer, cancer stage, year of diagnosis, level of education according to Census tract, income above or below the poverty line according to Census tract, score on the comorbidity index, number of provider visits within the 12 months before diagnosis, presence or absence of osteoporosis, osteopenia, or fracture within the 12 months before diagnosis, and presence or absence of treatment with radical prostatectomy or radiation therapy. Outcomes were censored at the time of death or a change from coverage under Medicare Parts A and B, or at the end of the follow-up period. Results for the SEER region, Census tract data on education and income, number of provider visits in the 12 months before diagnosis, and presence or absence of osteoporosis, osteopenia, or fracture within the 12 months before diagnosis are not presented.

<sup>‡</sup> The number of doses signifies doses received within the 12 months after diagnosis for patients in whom treatment with gonadotropin-releasing hormone agonists was initiated within 6 months after the diagnosis.

interval, 1.18 to 1.48). The relative risk of fracture related to androgen-deprivation therapy decreased with an increasing score on the modified Charlson comorbidity index.<sup>18,19</sup> For instance, the relative risk of fracture with nine or more doses of gonadotropin-releasing hormone agonist was 1.62 (95 percent confidence interval, 1.48 to 1.76) for a score of 0 on the comorbidity index, but it was 1.03 (95 percent confidence interval, 0.82 to 1.31) for a score of 3 or more on the comorbidity index. The full model for these interactions is presented in the Supplementary Appendix.

**NUMBERS NEEDED TO HARM**

The number needed to harm for the occurrence of any fracture during the period 12 to 60 months after the diagnosis of prostate cancer was 28 (95 percent confidence interval, 26 to 31) for any use of a gonadotropin-releasing hormone agonist and 16 (95 percent confidence interval, 13 to 19) for orchiectomy. Because the relative risk of fracture varied according to the age of the subject and the total number of doses of gonadotropin-releasing hormone agonist received in the year after diagnosis, this relationship was expressed by calculating the number needed to harm according to age and number of doses (Table 4). There was a pattern of lower numbers needed to harm with an increasing total number of doses of gonadotropin-releasing hormone agonist administered and with increasing age. For example, the number needed to harm was 74 (95 percent confidence interval, 50 to 146) among those 66 to 69 years of age who received one to four doses of a gonadotropin-releasing hormone

agonist during the year after receiving the diagnosis of prostate cancer, whereas it was 12 (95 percent confidence interval, 11 to 13) among those 80 years of age or older who received nine or more doses during the same period.

DISCUSSION

We found that androgen-deprivation therapy is associated with an increase in the risk of fracture among older men with prostate cancer. The risk increases with the number of doses of a gonadotropin-releasing hormone agonist administered during the first year after diagnosis. This study provides an estimate of the risk of fracture that is attributable to androgen-deprivation therapy by including patients who were not treated with androgen deprivation and adjusting for confounding variables.

The hazard ratios we found were moderate but could nevertheless be clinically important, given the substantial underlying rate of fracture in our study population, which consisted of elderly men. Given an annual incidence of prostate cancer of more than 220,000, given that more than 40 percent of patients receive gonadotropin-releasing hormone agonists as an initial treatment,<sup>5,6</sup> and given a number needed to harm of 28, approximately 3000 excess fractures per year would be attributable to the use of treatment with gonadotropin-releasing hormone agonists.

Several confounding factors may account for the apparent risk of fracture related to androgen deprivation. Older age and more advanced stages of cancer are associated with both androgen-deprivation treatment<sup>4</sup> and fracture.<sup>29</sup> In addition, patients who are about to undergo androgen-deprivation therapy tend already to have lower bone-mineral density.<sup>12,30</sup> However, the association between androgen deprivation and fracture remained after extensive adjustment for known confounders and preexisting bone disease, and our results have biologic plausibility. Both orchiectomy and gonadotropin-releasing hormone agonists accelerate bone loss,<sup>29,31</sup> and low bone-mineral density is strongly associated with an increased risk of fracture.<sup>32</sup> Moreover, there was a significant dose-response relation between the number of doses of gonadotropin-releasing hormone agonists administered and the risk of fracture.

A limitation of the study was that we did not exclude from the analysis fractures that were related to bone metastases. However, only 7 to 16 percent

**Table 4. Estimated Number Needed to Harm for the Occurrence of Any Fracture within 12 to 60 Months after Diagnosis, According to Age and Extent of Androgen Deprivation.\***

Age	Gonadotropin-Releasing Hormone Agonist			Orchiectomy
	1-4 doses	5-8 doses	≥9 doses	
	no. needed to harm (95% CI)			
66-69 yr	74 (50-146)	42 (29-73)	18 (16-24)	15 (13-18)
70-74 yr	69 (46-146)	39 (27-71)	17 (15-20)	14 (12-17)
75-79 yr	61 (41-125)	34 (24-61)	15 (14-17)	13 (11-15)
≥80 yr	46 (32-91)	26 (19-45)	12 (11-13)	10 (9-11)

\* Estimates were calculated on the basis of adjusted rates of fracture five years after diagnosis from a Cox model with any fracture as the outcome. Doses of a gonadotropin-releasing hormone agonist were grouped according to the number of doses received within the 12 months after diagnosis. CI denotes confidence interval.

of the fractures in prostate cancer are secondary to bone metastases.<sup>14,15</sup> In addition, the risk of fracture associated with androgen-deprivation therapy was not reduced when the analysis was restricted to patients with early-stage cancer, who would be less likely to have bone metastases. Another limitation was that we restricted our analysis to the risk of fracture associated with the number of doses of a gonadotropin-releasing hormone agonist given in the first year after diagnosis. Longer periods of exposure to gonadotropin-releasing hormone agonists may be associated with a higher risk of fracture.<sup>33</sup>

One important implication of this study concerns the assessment of the risks and benefits of androgen-deprivation therapy. There was a dramatic increase in the use of such therapy during the 1990s<sup>4-6</sup> (Table 1). The reasons for this increase may include demonstrated efficacy in patients with locally advanced cancer, the financial incentives to providers, and the urge, on the part of physicians and patients, to do something in the face of a rising PSA level. Our findings, along with those of smaller clinical series,<sup>13-15</sup> underscore that such treatment is not benign. The risk of fracture and other toxic effects should therefore figure prominently in discussions between physician and patient with regard to the decision to initiate androgen-deprivation therapy, particularly in settings where its efficacy is uncertain. Most of the patients in whom androgen deprivation is used as the primary therapy have localized prostate cancer,<sup>4</sup> and gonadotropin-releasing hormone agonists are commonly prescribed for patients with a rising PSA level after radical prostatectomy. Yet there is no evidence from

clinical trials of a survival benefit for androgen-deprivation therapy in either of these settings.<sup>1</sup>

A second implication is that trials of interventions to lower the risk of fracture among patients with prostate cancer are needed. Parenterally administered bisphosphonates have been shown to prevent the loss of bone-mineral density after androgen-deprivation therapy for prostate cancer.<sup>34,35</sup> Current recommendations are that men with prostate cancer who are being treated with androgen deprivation should have their bone-mineral density monitored and should commence bisphosphonate therapy if osteoporosis develops or a fracture occurs.<sup>16</sup> Large prospective trials are required to assess the efficacy and the cost-effectiveness of bisphosphonate treatment to reduce the risk of fracture among men receiving androgen-deprivation therapy.

In conclusion, our study shows that androgen deprivation in the form of orchiectomy or treatment with gonadotropin-releasing hormone agonists is associated with an increased risk of fracture in patients with prostate cancer. This finding underscores the need for caution in the use of these therapies in settings without clear evidence of a benefit. Trials of therapies such as bisphosphonates to lower the risk of fracture are needed in patients for whom gonadotropin-releasing hormone agonists are clearly indicated.

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