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HIP FRACTURES IN MEN WITH PROSTATE CANCER TREATED WITH ORCHIECTOMY

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ABSTRACT

Purpose: Androgen deprivation therapy increases the risk of osteoporosis related fractures. This issue is of increasing importance in men with prostate cancer as increasingly more undergo androgen deprivation therapy and therapy is administered sooner following diagnosis. Data directly addressing the long-term fracture risk in men diagnosed with prostate cancer are limited.

Materials and Methods: Using population based registries in Sweden we studied the incidence of hip fractures in 17,731 men diagnosed with prostate cancer from 1964 to 1996 who were treated with bilateral orchiectomy within 6 months of diagnosis. The fracture incidence was compared to the incidence in 43,230 men diagnosed with prostate cancer but not treated with orchiectomy and in 362,354 of similar age who were randomly selected from the general population.

Results: Men treated with orchiectomy were at increased risk for hip fracture. The estimated relative risk comparing men who underwent orchiectomy to population controls was 2.11 (95% CI 1.94 to 2.29) for femoral neck fractures and 2.16 (95% CI 1.97 to 2.36) for intertrochanter fractures. An increased risk of hip fracture was observed as early as 6 months after orchiectomy and the relative risk remained fairly constant up to 15 years following orchiectomy.

Conclusions: Hip fracture risk increases almost immediately following orchiectomy and the excess risk persists for at least 15 years. This side effect should be considered when assessing the merits of androgen deprivation therapy, particularly in symptom-free men diagnosed with localized prostate cancer. Measures to prevent osteoporosis should be considered in men undergoing androgen deprivation therapy.

KEY WORDS: prostate, androgen antagonists, fractures, orchiectomy, prostatic neoplasms

Osteoporosis related fractures are an important complication of androgen deprivation therapy in men with prostate cancer.[1,2] Androgen deprivation can be achieved surgically by bilateral orchiectomy or medically, eg by treatment with gonadotropin-releasing hormone agonists. The relationship between hypoganadism and osteoporosis has been appreciated for decades and a decreased incidence of femur neck fracture has been observed in women on hormone replacement therapy but only recently has research focused on osteoporosis and its consequences in men undergoing androgen deprivation therapy.[3]

Androgen deprivation therapy is associated with decreased bone mineral density in men diagnosed with prostate cancer[1] as well as in young men castrated following sexual offenses.[4] Men treated with androgen deprivation therapy for prostate cancer have been shown to be at increased risk for bone fracture, although previous studies have been relatively small.[5–11]

The incidence of localized prostate cancer is increasing in many countries, partly due to the effect of prostate specific antigen screening. Androgen deprivation therapy, previously used primarily in men with metastatic prostate cancer, is being administered in an increasing proportion of men diagnosed with nonmetastatic prostate cancer, who have relatively long life expectancy, and therapy is commencing sooner following diagnosis. Therefore, total time spent with castrate levels of testosterone in men diagnosed with prostate cancer is increasing. Thus, the prevention of osteoporosis related fractures, which are associated with considerable morbidity and mortality, is an increasingly important issue.

Using population based registries available in Sweden we examined the incidence of various bone fractures in 17,731 men diagnosed with prostate cancer treated with bilateral orchiectomy. The fracture incidence was compared to the incidence in 43,230 men diagnosed with prostate cancer but not treated with orchiectomy and in 362,354 of similar age who were randomly selected from the general population. We estimated the increase in fracture risk associated with androgen deprivation therapy and studied how fracture risk depends on time since the commencement of therapy, calendar period and patient age.

METHODS

The unique national registration number assigned to all Swedish residents is used to index almost all registries in Sweden, including the cause of death registry, cancer registry, registry of total population and hospital inpatient registry.[12] The population based Swedish Cancer Registry commenced in 1958. Notification of all newly diagnosed cancers is mandatory for pathologists/cytologists and physicians. Approximately 96% of all incident cancers are reported to the Swedish Cancer Registry and 98% of those reported are histologically verified.[13] The Swedish Cancer Registry does not record information on stage or treatment. Individual information on inpatient care has been documented county-wise in the inpatient register since 1964,

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when 6 of the 26 Swedish counties provided data. Of the 26 counties 20 reported all inpatient care to the register in 1984 and coverage has been nationwide since 1987.[14]

Using the cancer register we identified all men diagnosed with prostate cancer between 1964 and 1996. For each man diagnosed with prostate cancer we randomly selected from the general population using the Registry of Total Population 5 of the same age residing in the same county and without a diagnosis of prostate cancer. The study was restricted to men diagnosed at a time when their county provided data to the inpatient registry since information on exposure (bilateral orchiectomy) and outcomes (fractures of the spine, pelvis, femoral neck, intertrochanter, thigh, lower leg, eg tibia or fibia, ankle, skull, skull base and face) was obtained by matching with the hospital inpatient registry.

Individuals were considered to enter the study (be at risk) 6 months following diagnosis of prostate cancer. Men diagnosed with prostate cancer who underwent bilateral orchiectomy within 6 months of diagnosis were classified into the orchiectomy group and men diagnosed with prostate cancer who were not treated with bilateral orchiectomy were classified into the no orchiectomy group. A third group contained population controls. Men who underwent bilateral orchiectomy 6 months or more following prostate cancer diagnosis were excluded from study. All men were followed until death, emigration, first diagnosis of the specific bone fracture or December 31, 1996. Each fracture was studied separately and only the first fracture of each bone was considered. We focused primarily on fractures of the femoral neck and intertrochanter since such fractures are relatively common and usually result in hospital admission.

We estimated the incidence proportion (cumulative incidence) for each bone fracture using the Kaplan-Meier method. We then modeled fracture incidence rates using Poisson regression to estimate incidence rate ratios (IRRs) and associated 95% CIs in each of the 2 groups of men diagnosed with prostate cancer compared to population controls. Estimates were adjusted for calendar period of diagnosis (grouped as 1960 to 1983, 1984 to 1991 and 1992 to 1996), time since entry (0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 7, 7 to 10, 10 to 14 and 15 or greater years) and attained age (0 to 64, 65 to 69, 70 to 74, 75 to 79, 80 to 84 and 85 or older). We used interaction terms in the model to investigate how the effect of exposure varied according to time since entry, calendar period of diagnosis and attained age.

We also estimated the relative excess risk[15] as a means of comparing fracture risk between the orchiectomy and no orchiectomy groups. Excess risk was estimated as the difference between the estimated fracture incidence rate in the specific group minus the estimated fracture incidence rate in population controls. We then calculated relative excess risk as the ratio of the 2 estimated excess risks.

Evaluation of model goodness of fit was performed using the deviance statistic, the study of deviance residuals and the study of interaction terms. All analyses were performed using the SAS system, version 8.02 (SAS Institute, Carey, North Carolina). We have a large material, meaning that even relatively small differences become statistically significant, so we do not emphasize the statistical significance of our results or report p values. Rather, we present 95% CIs as measures of statistical precision. Data from the various registries were matched at the Swedish National Board of Health and Welfare, and were provided to us without personal identifiers. As such, ethics committee approval was not required.

RESULTS

The study included 17,731 men with prostate cancer treated with bilateral orchiectomy within 6 months of diagnosis (table 1). Median time from diagnosis to orchiectomy in these men was 40 days (mean 51). The study also included 43,230 men diagnosed with prostate cancer but not treated with bilateral orchiectomy and 362,354 population controls. The number of orchiectomies performed yearly varied with calendar time, reflecting trends in the preferred type of androgen deprivation therapy (fig. 1). Figure 1 underestimates the total number of orchiectomies performed in Sweden since men were required to survive 6 months or longer following diagnosis to enter our study. When assessing trends in the number of orchiectomies with time, it must be considered that not all counties provided data to the inpatient registry prior to 1987.

Table 2 shows estimated incidence rate ratios for each of the 2 groups of men diagnosed with prostate cancer compared to controls. We observed an approximately double risk of fractures of the spine, pelvis, femoral neck, intertrochanter, thigh and lower leg in men treated with orchiectomy compared to population controls. Men diagnosed with prostate cancer who did not undergo orchiectomy were also at increased risk for these bone fractures compared to population controls, although the increase in risk was not of the same magnitude as in men treated with orchiectomy.

Fractures of the femoral neck and intertrochanter were the most common fractures observed during followup. Table 3 shows incidence rate ratios for these 2 fractures estimated separately for various time intervals since entry. An increased risk was observed from the first interval, which covers the period of 6 to 18 months following diagnosis, and relative risks remained at a similar level throughout followup. This feature could be seen in plots of cumulative incidence (figs. 2 and 3), although cumulative incidence estimates were not adjusted for potential confounding factors. The incidence proportion of femoral neck fractures 10 years following diagnosis was 12% in men treated with orchiectomy and 5% in men without a diagnosis of prostate cancer (fig. 2). The corresponding values for intertrochanter fractures were 9% and 4% (fig. 3).

The estimated relative risks of femoral neck and intertrochanter fractures decreased with increasing patient age (table 4). This is because the baseline fracture incidence rate increased with age (table 5). Because there were fewer fractures in the younger age groups, the estimated relative risks reported in other tables is weighted toward the estimates for the older age groups. The ratios of excess risks (ie relative excess risks) were similar for each age group (table 5). There was some evidence that the relative risks in men treated with and without orchiectomy increased with calendar time (table 6). Study of the underlying incidence rates showed that incidence increased with time in men treated with orchiectomy, remained stable in men treated without orchiectomy and decreased in population controls (data not shown).

DISCUSSION

We found that men treated with orchiectomy as a means of androgen deprivation were at increased risk for hip fracture. Increased risk was observed as early as 6 months after orchiectomy and the relative risk remained fairly constant up to 15 years following orchiectomy. The relative risk was higher in younger than in older men. Restricting analysis to men diagnosed in 1992 or later did not alter the findings.

Fractures can be broadly classified as osteoporotic or pathological, or due to major trauma. We do not have information on the underlying cause of the observed fractures and in particular we could not identify pathological fractures, which are caused by tumor growth in the bone. There is no reason to believe that men diagnosed with prostate cancer are at higher risk for major trauma than population controls, and so including fractures due to major trauma would have attenuated relative risk estimates. During the late 1970s and early 1980s, before the era of prostate specific antigen screen-

TABLE 1. *Characteristics of individuals in study*

Characteristics	Orchiectomy	No Orchiectomy	Controls
No. individuals	17,731	43,230	362,354
No. at risk for femoral fracture after (yrs):			
1	13,443	33,508	313,113
2	9,909	25,682	267,309
5	4,029	11,292	156,752
10	577	2,536	50,366
15	30	498	12,041
No. age at entry (%):			
64 or Younger	1,583 (9)	6,797 (16)	46,984 (13)
65–69	2,463 (14)	7,380 (17)	56,919 (16)
70–74	4,193 (24)	10,381 (24)	85,671 (24)
75–79	4,720 (27)	9,478 (22)	84,155 (23)
80–84	3,350 (19)	6,245 (14)	59,216 (16)
85 or Older	1,422 (8)	2,949 (7)	29,409 (8)
Age at entry:			
Mean	75	73	74
Median	75	73	74
SE	0.06	0.04	0.01
Range	44–97	38–98	38–101
No. entry yr (%):			
1964–1983	2,547 (14)	9,373 (22)	82,270 (23)
1984–1991	11,139 (63)	16,015 (37)	162,945 (45)
1992–1996	4,045 (23)	17,842 (41)	117,139 (32)
No. fractures during followup:			
Spine	195	253	2,833
Pelvis	122	181	2,318
Femur neck	604	920	9,956
Intertrochanter	491	701	7,772
Thigh	37	45	407
Lower leg (tibia, fibia)	41	61	693
Ankle	21	39	475
Skull	7	12	155
Skull base	14	23	258
Face	29	66	746
Totals	1,561	2,301	25,613
Person-yrs at risk:			
Mean	3.38	3.59	
Median	2.51	2.58	
SE	0.02	0.01	
Range	0–25	0–29	
Yrs from entry to death during followup:			
Mean	2.80	3.46	5.31
Median	2.05	2.42	4.23
SE	0.02	0.02	0.01
Range	0–18	0–29	0–30
No.	13,469	22,044	
Yrs from entry to first bone fracture:			
Mean	3.26	5.47	4.95
Median	2.60	4.41	3.93
SE	0.07	0.13	0.03
Range	0–17	0–23	0–26

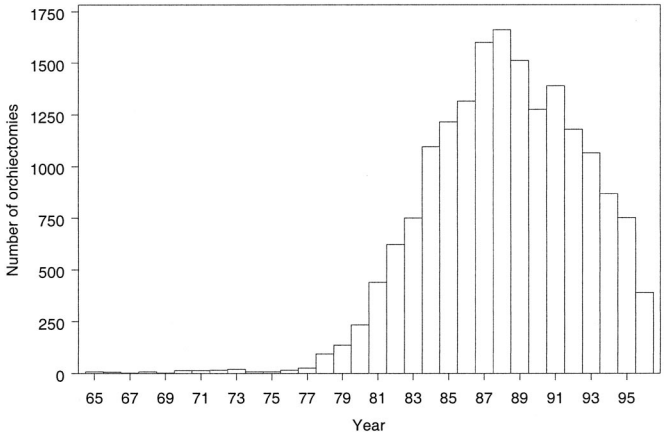

FIG. 1. Number of orchiectomies in men in study for each calendar year from 1965 to 1996.

TABLE 2. *Estimated IRRs of fracture risk in men diagnosed with prostate cancer (treated with and without orchiectomy) vs men without prostate cancer*

	No Orchiectomy		Orchiectomy	
	IRR	95% CI	IRR	95% CI
Spine	1.26	1.10–1.43	2.34	2.02–2.71
Pelvis	1.15	0.99–1.34	1.79	1.49–2.15
Femur neck	1.35	1.26–1.44	2.11	1.94–2.29
Intertrochanter	1.33	1.23–1.44	2.16	1.97–2.36
Thigh	1.54	1.13–2.10	3.52	2.49–4.95
Tibia, fibia	1.18	0.90–1.53	2.16	1.57–2.97
Ankle	0.99	0.71–1.37	1.78	1.14–2.77
Skull	0.97	0.54–1.76	1.52	0.71–3.26
Skull base	1.24	0.81–1.91	1.91	1.11–3.29
Face	1.18	0.91–1.51	1.34	0.93–1.95
Skull + face	1.21	0.98–1.49	1.54	1.15–2.06

Estimates are adjusted for attained age, time since entry, and calendar period at diagnosis.

ing, approximately a quarter of men diagnosed with prostate cancer in Sweden had metastatic disease at diagnosis.[16] Androgen deprivation is a common therapy in men diagnosed with metastatic prostate cancer and we would expect that the group treated with orchiectomy would have contained a larger proportion with metastatic disease at diagnosis compared to the group that did not undergo orchiectomy. As such, we might have expected a higher incidence of patho-

TABLE 3. *IRRs estimated separately for each period since entry at 6 months following diagnosis*

Yrs Since Entry	No Orchiectomy		Orchiectomy	
	IRR	95% CI	IRR	95% CI
Femur neck:				
0–1	1.45	1.25–1.68	1.81	1.50–2.19
1–2	1.39	1.18–1.64	2.07	1.71–2.52
2–3	1.42	1.19–1.71	2.41	1.96–2.96
3–4	1.08	0.86–1.36	2.18	1.72–2.77
4–5	1.32	1.04–1.67	2.55	1.97–3.28
5–7	1.41	1.17–1.71	2.10	1.66–2.66
7–10	1.32	1.07–1.63	2.17	1.65–2.87
10–14	1.20	0.90–1.59	1.27	0.68–2.37
15 or Greater	1.32	0.77–2.26	5.61	1.40–22.6
Intertrochanter:				
0–1	1.74	1.48–2.06	2.38	1.95–2.90
1–2	1.42	1.18–1.71	1.84	1.46–2.32
2–3	1.07	0.84–1.35	2.27	1.80–2.87
3–4	1.22	0.95–1.57	2.73	2.13–3.50
4–5	1.22	0.93–1.59	1.70	1.22–2.37
5–7	1.21	0.97–1.51	2.01	1.55–2.61
7–10	1.13	0.88–1.45	1.90	1.39–2.60
10–14	1.32	0.97–1.81	2.96	1.90–4.62
15 or Greater	1.64	0.98–2.77	2.86	0.40–20.4

Estimates were obtained using interaction terms in Poisson regression model and are adjusted for attained age and calendar period at diagnosis.

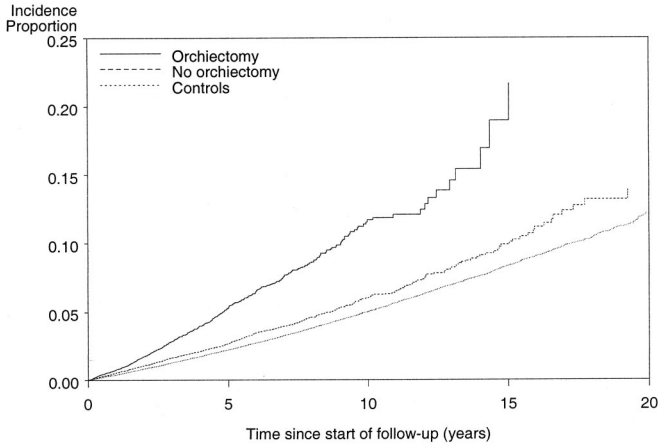

FIG. 2. Incidence proportion of femoral neck fractures in each of 3 exposure groups as function of time since start of followup (6 months after diagnosis).

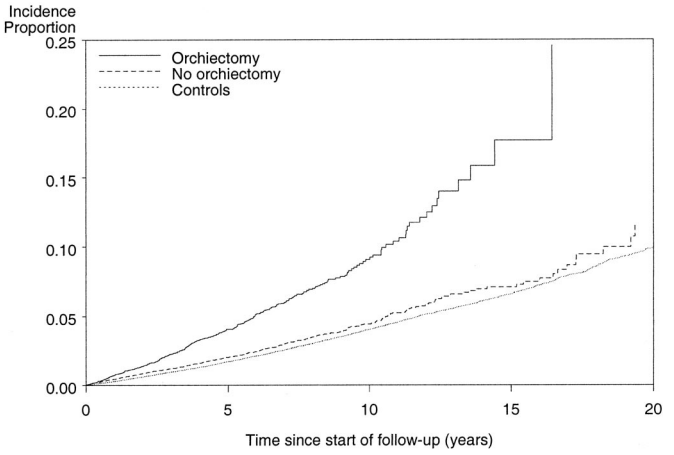

FIG. 3. Incidence proportion of intertrochanter fractures in each of 3 exposure groups as function of time since start of followup (6 months after diagnosis).

TABLE 4. *IRRs and 95% CIs estimated separately according to attained age*

Attained Age	No Orchiectomy		Orchiectomy	
	IRR	95% CI	IRR	95% CI
Femur neck:				
0–64	3.71	2.36–5.81	7.63	3.92–14.9
65–69	2.05	1.44–2.92	6.66	4.55–9.75
70–74	1.35	1.09–1.68	2.93	2.27–3.79
75–79	1.44	1.24–1.67	2.52	2.12–2.99
80–84	1.27	1.12–1.45	1.91	1.64–2.22
85 or Older	1.26	1.12–1.41	1.63	1.40–1.89
Intertrochanter:				
0–64	2.81	1.68–4.72	10.80	5.94–19.8
65–69	1.75	1.22–2.53	4.39	2.82–6.82
70–74	1.57	1.23–2.00	3.65	2.78–4.80
75–79	1.26	1.06–1.50	2.28	1.87–2.78
80–84	1.29	1.11–1.50	1.77	1.48–2.12
85 or Older	1.24	1.08–1.41	1.89	1.62–2.21

Estimates were obtained using interaction terms in Poisson regression model and are adjusted for calendar period and time since entry.

logical fractures in the group of men who underwent orchiectomy. However, men diagnosed with metastatic prostate cancer have a poor prognosis, and so most pathological fractures would occur within a year or 2 following diagnosis. By excluding the first 6 months of followup following diagnosis we excluded men in whom tumor was diagnosed as a result of a fracture as well as men who experienced fracture within 6 months of diagnosis. We observed approximately constant relative risks throughout followup, suggesting that our estimates were not heavily influenced by the occurrence of pathological fractures. Skeletal metastases are more common in the vertebrae and pelvis than in the hip, so that if our estimates were heavily influenced by pathological fractures, we would have expected larger relative risks for these bones, which we did not observe.

The methods of diagnosing and treating prostate cancer have changed with time. We observed similar patterns of relative fracture risk when analyses were restricted to individuals diagnosed in 1992 or later, eg relative risk estimates were similar for each time interval since entry. However, the absolute fracture risk during this period was slightly higher in men who underwent orchiectomy and slightly lower in population controls, leading to slightly higher estimates of relative risk. During the 1990s compared to earlier years a smaller proportion of men diagnosed with prostate cancer had metastatic disease at diagnosis. As such, we would have expected the influence of pathological fractures on the relative fracture risk comparing men with and without orchiectomy to be smaller during this period. That is, we would have expected the estimated relative risks to be larger for this period, which is exactly what we observed. Estrogen therapy, which is thought to protect against osteoporosis,[17] was commonly used as a means of androgen deprivation during 1964 to 1983, so that we might have expected patients diagnosed with prostate cancer to be at decreased fracture risk compared to population controls during this period, which we did not observe.

The observed difference in fracture risk between, for example, men treated with orchiectomy and population controls cannot be completely attributed to osteoporotic fractures secondary to orchiectomy. Other factors that affect fracture risk, the probability of being treated as an inpatient when a fracture is diagnosed, the probability that a diagnosed fracture is recorded in the inpatient registry or selection into the groups that we studied should be considered. It is reasonable to believe that most individuals with a hip fracture have the fracture diagnosed and are admitted to the hospital for surgery. On the other hand, vertebral fractures are not always diagnosed and even when a vertebral fracture is diagnosed, the patient is not always admitted to the hospital. For most fracture types including those of the hip, we believe that the sensitivity and specificity of recording fractures was similar in the 3 study groups. Therefore, we argue that our relative risk estimates should not be substantially biased.

TABLE 5. *Fractures, person-years at risk and estimated incidence rates for femoral neck and intertrochanter fractures stratified by attained age*

Attained Age	Controls			No Orchiectomy			Orchiectomy			Relative Excess Risk*
	No. Fractures	Person-Yrs at Risk	Rate/10,000 Person-Yrs	No. Fractures	Person-Yrs at Risk	Rate/10,000 Person-Yrs	No. Fractures	Person-Yrs at Risk	Rate/10,000 Person-Yrs	
Femoral neck:										
0–64	64	132,709	5	27	15,118	18	10	2,746	36	2.4
65–69	179	216,856	8	37	21,854	17	31	5,700	54	5.3
70–74	741	377,201	20	92	34,708	27	64	11,229	57	5.4
75–79	1,713	472,572	36	201	38,563	52	141	15,602	90	3.4
80–84	2,792	409,415	68	252	29,100	87	177	13,755	129	3.3
85 or Older	4,005	297,026	135	311	18,408	169	181	8,344	217	2.4
Intertrochanter:										
0–64	59	132,685	4	19	15,140	13	13	2,745	47	5.3
65–69	192	216,849	9	34	21,870	16	22	5,714	38	4.4
70–74	528	377,435	14	76	34,740	22	57	11,252	51	4.6
75–79	1,411	473,215	30	144	38,662	37	106	15,672	68	5.1
80–84	2,141	411,140	52	194	29,236	66	128	13,856	92	2.8
85 or Older	3,101	298,832	104	234	18,535	126	165	8,399	196	4.1

* Estimated excess risk ratio in men with prostate cancer who did vs did not undergo orchiectomy.

TABLE 6. *IRRs and 95% CIs estimated separately for each calendar period*

Calendar Period	No Orchiectomy		Orchiectomy	
	IRR	95% CI	IRR	95% CI
Femur neck:				
1964–1983	1.22	1.08–1.37	2.00	1.64–2.44
1984–1991	1.37	1.25–1.52	2.05	1.85–2.27
1992–1996	1.56	1.34–1.82	2.52	2.04–3.11
Intertrochanter:				
1964–1983	1.25	1.08–1.44	1.84	1.44–2.36
1984–1991	1.30	1.17–1.45	2.17	1.94–2.42
1992–1996	1.52	1.27–1.81	2.52	1.99–3.19

Estimates were obtained using interaction terms in Poisson regression model and are adjusted for attained age and time since entry.

Androgen deprivation therapy is being administered in an increasing proportion of men diagnosed with localized prostate cancer who have relatively long life expectancy and therapy is commencing sooner following diagnosis. Our finding that hip fracture risk increases almost immediately following orchiectomy and excess risk persists for at least 15 years suggests that the increased risk of hip fracture should be considered when assessing the merits of androgen deprivation therapy, particularly in symptom-free men diagnosed with localized prostate cancer. The potential benefits of improved survival associated with androgen deprivation therapy in men with localized prostate cancer must be weighed against the potential side effects, including an increased risk of osteoporosis and osteoporotic fractures. Measures to prevent osteoporosis should be considered in men undergoing androgen deprivation therapy and proposed prevention strategies include lifestyle modifications, supplemental calcium and vitamin D,[2] and decreased vitamin A.[18] Recent evidence suggests that biphosphonates may be beneficial for preventing bone loss during androgen deprivation therapy, although further studies in this area are required.[3,19]

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