Fracture risk in androgen deprivation therapy: a Canadian population based analysis

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Introduction: *Prostate cancer is the most common noncutaneous malignancy diagnosed in men. The use of androgen deprivation therapy (ADT) is the mainstay of treatment for metastatic disease. The use of ADT has been reported to increase the risk of osteoporosis in men with prostate cancer, with higher risk of fracture than age matched controls. We sought to confirm the higher fracture risk of men with prostate cancer on ADT in the Canadian population.*
Methods: *We used the Population Health Research Data Repository housed at Manitoba Centre for Health Policy to identify all cases of fractures of the hip, vertebra, or wrist in men aged 50 years and older occurring between 1996 and 2004. Each case was matched with up to three controls by age, sex, ethnicity and medical comorbidity. We calculated the odds ratios (OR) for fracture with prostate cancer, and with or without ADT, after adjusting for possible confounding variables.*
Results: *There were 4696 cases of fracture matched with 14080 controls. After controlling for confounding variables, there was no significant association between prostate cancer and fracture risk (adjusted OR = 0.97, 95% confidence intervals [CI]: 0.83-1.15). We detected a significant association between ADT and fracture risk in men. The adjusted ORs for current and past ADT usage were 1.71 (95% CI: 1.13 - 2.58) and 2.42 (95% CI: 1.42-4.12) respectively.*
Conclusion: *Our findings suggest that prostate cancer itself does not increase the risk of fracture and corroborate published results demonstrating an association between ADT and fractures.*

Key Words: fracture, osteoporosis, prostate cancer, androgen deprivation therapy

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Introduction

Osteoporosis affects at least one in eight Canadian men over age 50, with one in four men having a fragility fracture in his lifetime.[1,2] Fragility fractures in men can impose considerable health care and economic burdens. The mortality rate in men is approximately double that in age matched women during the first 6 months after a fracture.[3,4]

Among the many risk factors for fragility fracture, age and hypogonadism are of particular concern in men with prostate cancer. One in seven men in Canada will be diagnosed with prostate cancer.[5] Over 70% of men with prostate cancer are older than 65,[5,6] a population already at risk for fragility fracture.[7] For men with metastatic disease, androgen deprivation

therapy (ADT) is the mainstay treatment. One in three men with prostate cancer will receive ADT,[8] which has proven to improve overall survival rate in those with advanced disease.[9-13] Nonetheless, skeletal complications are an important adverse effect associated with ADT induced hypogonadism. Testosterone and estrogen hormones exert antiapoptotic effects on osteoblasts and osteocytes, and proapoptotic effects on osteoclasts.[14] Testosterone and estrogen deficiencies result in increased rate of bone resorption. During ADT, serum testosterone and estrogen fall below the normal levels. There is significant bone mineral density (BMD) loss, which begins as early as the first 6 to 12 months of ADT.[15,16] Recent studies found that the associated fracture risk increased by 37% in men with prostate cancer on ADT.[17-19] There is also evidence suggesting fractures increase the mortality rate of men with prostate cancer.[20] Furthermore, a recent study indicates that hormone naïve men may have low BMD even prior to starting ADT.[21]

Previous studies are heterogeneous and may not be representative of the Canadian population. Therefore, we investigated fracture risk in men with prostate cancer who were on ADT in a population based analysis.

Research design and methods

Data sources

A retrospective, case control study was conducted using de-identified administrative health data from the Population Health Research Data Repository housed at Manitoba Centre for Health Policy (MCHP) of the University of Manitoba. The Repository contains comprehensive healthcare utilization data for nearly all Manitoba residents.[22] The Repository databases are representative of the population of Manitoba, since there is free and comprehensive health care coverage for essentially all residents of the province of Manitoba. Each resident is assigned an encrypted unique personal health identification number (PHIN), which allows for linkage across datasets and creation of person specific longitudinal records of health service utilization.

The Repository includes administrative health data from inpatient and outpatient services, and all dispensations of prescription medications. For every inpatient hospital encounter, up to 16 diagnoses are recorded and coded according to International Classification of Disease-9-Clinical Modification (ICD-9-CM) with five digit diagnoses. Every outpatient encounter is coded with a single three digit ICD-9 diagnosis code. The inpatient and outpatient databases contain information from the year 1970 until present. The prescription medication database, Drug Program Information Network (DPIN), contains all outpatient pharmacy prescription medication dispensation records since April 1, 1995. Each record includes the medication identification, date of dispensation, strength, route and dosage form, number of dosage, and prescription duration. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) system of the WHO.[23] The administrative health databases, including inpatient and outpatient databases, and the DPIN have been validated for accuracy in a wide range of clinical disorders including fractures.[24-31]

Study population

All men aged 50 years or older who were seen by a physician or admitted to hospital between April 1, 1996 to March 31, 2004 with a diagnosis of vertebral fracture without cord injury (ICD-9-CM code 805), wrist fracture (ICD-9-CM code 813) or hip fractures (ICD-9-CM code 820-821) were included as cases. Hip fractures had to be accompanied by a physician claim for a site specific fracture reduction or fixation. Age was obtained from the Manitoba Health registry file as of the first date of fracture. Individuals who were using osteoprotective medications in the year prior to the case index date, residents of personal care homes, and those with interrupted health services coverage were excluded.

Each fracture case was randomly matched to up to three controls with no history of vertebral, hip, or wrist fracture. Matching variables were: age (within 5 years the case's age); ethnicity (Aboriginal or non-Aboriginal from provincial and national systems); and comorbidity (determined form the Johns Hopkins Ambulatory Care Group system[32] in the year prior to the index date). The comorbidity index uses the number of ambulatory diagnostic groups (ADGs) subdivided into four categories: scores of 0, 1-2, 3-5, or 6 or more. The ADG system has been validated for quantifying medical comorbidity and fracture risks.[26,33]

Assessment of medication use

ADT use was determined through the Manitoba pharmacy database using the ATC codes G03G (gonadotropins and other ovulation stimulants) and L02BB (antiandrogens which includes flutamide). Exposure to ADT drugs was categorized as non use, past use and current use. Current use was at least one dispensation from the drug category within 120 days preceding the index date of the fracture case. Past use was at least one dispensation in the 121-365 days

preceding the fracture case index date. Non use was no recorded dispensations within the 365 days prior to the fracture case index date.

Ascertainment of potential confounders

Potential confounders included in this study were variables that could be accessed from the administrative data and which had been previously associated with risk of fractures.[34] In particular, we controlled for specific diagnostic definitions from ICD-9-CM codes from physician office visits and/or hospitalizations or both found during the 3 years prior to case fracture index date: hypertension, diabetes, ischemic heart disease (these three diagnoses were used as proxies for obesity), corticosteroid use, myocardial infarction, epilepsy, rheumatoid arthritis, solid organ transplant, chronic obstructive pulmonary disease, substance abuse, depression, dementia, schizophrenia and home care use from the home care database (as a proxy for frailty). Finally, we also identified and controlled for a prior diagnosis of prostate cancer.

Regions of residence (rural north, rural south and the urban centre of Winnipeg) and neighborhood income quintiles were used to describe cases and control subjects. Mean household income for dissemination areas (DAs) was obtained from 2001 Statistics Canada Census public use files; DAs are the smallest geographic unit for which Census data are provided. These data were used to define quintiles (five groupings of about 20% of the population each; income quintile groupings were from 1 [lowest] to 5 [highest], stratified separately for urban and rural residency).[35] Income quintiles were later aggregated into lower income (two lowest quintiles) and higher income (three highest quintiles) in the statistical analyses.

Statistics

Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for fracture in ADT users. ORs were partially adjusted for sociodemographic variables (area of residence and income), and then fully adjusted for multiple medical diagnoses (including prostate cancer diagnosis) and use of home care services. We determined an OR to be statistically significant if the 95% confidence interval did not include unity. All regression analyses were performed using the SAS version 9.1.3.[36]

Results

A total of 4696 cases met our fracture case definition between April 1996 and March 2004 and were matched to 14080 nonfracture controls. Baseline characteristics of cases and controls, and the unadjusted univariate ORs for the association between each variable and fracture, are shown in Table 1.

There were 1074 men with a diagnosis of prostate cancer in our study population, representing 276 (5.9%) of 4696 fracture cases, and 798 (5.7%) of 14080 nonfracture controls. There were 276 cases (25.7%) of fracture among 1074 men with prostate cancer, as compared to 4420 cases (25.0%) of fracture among 17702 men without prostate cancer. There was no significant association of fracture and prostate cancer diagnosis (unadjusted OR = 1.04 [95% CI: 0.90-1.19]).

There were 193 men who were ADT users in our study population: 70 (1.5%) of 4696 fracture cases, and 123 (0.9%) of 14080 nonfracture controls. There were 28 cases (42.4%) of fracture of 66 men who were past ADT users, and 42 cases (33.1%) of fracture of 127 men who were current ADT users, as compared to 4626 cases (24.9%) of fracture out of 18583 men who did not receive ADT. There were significant associations between past ADT usage and fractures (unadjusted OR = 2.21 [95% CI: 1.35-3.60]) and between current ADT usage and fractures (unadjusted OR = 1.48 [95% CI: 1.02-2.15]).

After controlling for the effects of sociodemographic variables, comorbid illnesses, and concurrent medications in a conditional logistic regression model, the fully adjusted ORs demonstrated significant associations with fracture for both past ADT use (adjusted OR = 2.42 [95% CI: 1.42-4.12]) and current ADT use (adjusted OR = 1.71 [95% CI: 1.13-2.58]), Table 2. A diagnosis of prostate cancer was not associated with fracture risk (adjusted OR = 0.97 [95% CI: 0.83-1.15]).

Discussion

Our population based study provides an assessment of the risk of osteoporotic fractures associated with ADT in Canadian men. Despite a lack of association between prostate cancer and fractures, there was increased fracture risk in men on both current and past ADT in both unadjusted and adjusted analyses. Our results corroborate previous findings of an association between ADT and fractures, though the risk ratios in our study (2.42 for past users, 1.71 for current users) are slightly higher than those of Shahinian et al.[17] (1.44 to 1.63).

Our study is the first to demonstrate fracture risk is not associated with prostate cancer. However, the association of prostate cancer and bone mineral density, a major contributing factor towards fracture risk, remains controversial. A recent prospective study has shown that total body bone mineral density was

TABLE 1. **Baseline characteristics and fracture risks**

	Fracture cases		**Non-fracture controls**		**Unadjusted odds ratio (95%CI)**
	n =	**4696**	**n =**	**14080**	
Age category (yrs)					
50-59	1196	25.5%	3630	25.8%	n/a
60-69	1006	21.4%	3013	21.4%	
70-79	1219	26.0%	3636	25.8%	
80 or older	1275	27.2%	3801	27.0%	
Number of ADGs*					
None	431	9.2%	1292	9.2%	n/a
1-2	1202	25.6%	3606	25.6%	
3-5	1694	36.1%	5082	36.1%	
6 or more	1369	29.1%	4103	29.1%	
Ethnicity					
Non-Aboriginal	4462	95.0%	13381	95.0%	n/a
Aboriginal	234	5.0%	699	5.0%	
Fracture site					
Vertebral	1412	30.1%	0	0.0%	n/a
Wrist	2049	43.6%	0	0.0%	
Hip	1235	26.3%	0	0.0%	
Residence					
Urban	2587	55.1%	7568	53.7%	1.02 (0.97-1.08)
Rural south	1942	41.4%	5967	42.4%	0.98 (0.92-1.04)
Rural north	167	3.6%	545	3.9%	0.92 (0.77-1.10)
Income level					
Lower	2180	46.4%	5939	42.2%	1.19 (1.11-1.27)
Higher	2516	53.6%	8141	57.8%	0.84 (0.79-0.90)
Medical comorbidity					
Epilepsy	27	0.57%	24	0.17%	3.37 (1.94-5.85)
Arthritis	74	1.58%	144	1.02%	1.54 (1.16-2.04)
Solid organ transplant	6	0.13%	19	0.13%	0.95 (0.38-2.37)
COPD	878	18.7%	2330	16.55%	1.13 (1.04-1.23)
Substance abuse	255	5.43%	350	2.49%	2.18 (1.85-2.58)
Depression	384	8.18%	708	5.03%	1.63 (1.43-1.85)
Schizophrenia	37	0.79%	55	0.39%	2.02 (1.33-3.06)
Dementia	319	6.79%	444	3.15%	2.15 (1.86-2.5)
Ischemic heart disease	798	16.99%	2543	18.06%	0.94 (0.86-1.03)
Myocardial infarction	248	5.28%	734	5.21%	1.01 (0.87-1.17)
Hypertension	1313	27.96%	4444	31.56%	0.89 (0.83-0.95)
Prostate cancer	276	5.9%	798	5.7%	1.04 (0.90-1.19)
ADT use					
Non users	4626	98.5%	13957	99.1%	Reference
Past users	28	0.6%	38	0.3%	2.21 (1.35-3.60)
Current users	42	0.9%	85	0.6%	1.48 (1.02-2.15)

*ADGs: ambulatory diagnostic groups

TABLE 2. **Adjusted odds ratios for fracture**

	OR (95% CI)	
	Partially adjusted model*	**Fully adjusted model****
ADT use		
Past users	2.25 (1.37-3.69)	2.42 (1.42-4.13)
Current users	1.51 (1.04-2.19)	1.71 (1.13-2.58)
Prostate cancer diagnosis	n/a	0.97 (0.83-1.15)

*Adjusted for area of residence and income level.
**Adjusted for above and home care service use, diagnosis of epilepsy, diabetes, ischemic heart disease, myocardial infarction, hypertension, rheumatoid arthritis, solid organ transplant, chronic obstructive pulmonary disease, substance abuse, depression, dementia, and schizophrenia.

inversely associated with risk of prostate cancer.[37] In the study, 5.6% of the 4597 men with no prior history of prostate cancer developed prostate cancer during follow up. There was a significant trend for decreasing prostate cancer risk with increasing bone mineral density quartiles. However, in another study by Cauley et al,[38] prostate cancer was associated with lower bone mineral density at both femoral neck and spine in the age adjusted analyses of 5995 men. The results from the Tobago Prostate Survey[39] and the Framingham Study[40] however, demonstrated that higher bone density was associated with an increased prostate cancer risk.

Our results regarding the association between ADT and fractures corroborate those of two US studies. In a large study, 50613 men with 66 years of age or older with prostate cancer who received ADT within 6 months after diagnosis were examined to see if ADT use was associated with increased risk of fracture. They found that 19.4% of those who received ADT had fractures as compared to 12.5% who did not receive ADT.[17] A similar study using a database of medical and pharmacy claims also showed increased relative risk of fracture in men receiving ADT as compared with men without ADT: relative risk 1.76 for hip fracture and 1.18 for vertebral fracture.[18]

Strengths of this study are the single public health provider, with comprehensive and integrated health service and prescription medicine databases that are well validated for many clinical disorders including fractures.[24-31] There are also some limitations of this research. Our analysis did not consider rates of orchiectomy in our population. Shahinian et al[17] showed that orchiectomy increases the risk of fracture, similar to gonadotropin releasing hormone agonists. Since some of the ADT non users may have undergone orchiectomy, this may have produced a bias towards the null (i.e., our ADT risk estimates are likely conservative and may be even higher than what we have reported). Anthropomorphic data, such as body mass index, current smoking status, functional level, cognitive and physical impairment scores cannot be directly assessed from the administrative data, though proxy variables were included where available. For example, we do not have data on obesity which may increase the risk or aggressiveness of prostate cancer but have a protective effect on bone. Instead, we use diabetes, hypertension, ischemia heart disease as a proxy for obesity. We are also unable to determine whether increased fracture risk from ADT relates to reduced bone mineral density, increased risk for falls, or fractures due to metastatic disease from our database. The latter may elevate the perceived risk of fracture from ADT. In any observational study there may be confounding factors due to unrecognized differences between cases and controls. For example, several studies suggest that 32%-75% of ADT naïve men with prostate cancer have pre-existing osteopenia or osteoporosis.[21,41-44]

There is mounting evidence of increased fracture risk in men with prostate cancer on ADT. The bone health in men with prostate cancer would be at further risk because corticosteroids have been commonly used as second line hormone therapy when ADT fails, and as combination with the standard chemotherapy for men with hormone refractory metastatic prostate cancer. Corticosteroids are known to cause bone loss and osteoporosis. It would be prudent to establish a standardized clinical practice guideline for BMD testing using dual energy x-ray absorptiometry (DXA) in this population. Currently, the Canadian Panel of the International Society for Clinical Densitometry (ISCD) recommends hypogonadal men should undergo BMD testing at baseline and at 12-24 months follow up.[45] However, clinical practice guidelines on BMD testing for men with prostate cancer on ADT vary

across Canada, from specific to general guidelines, with no established guidelines at all in most provinces. For instance, Alberta Cancer Board has a very specific guideline that recommends baseline DXA scan for all patients undergoing long term ADT of more than 6 months, with 12 months and 6 months follow up DXA scans for those with baseline normal BMD and osteopenia respectively.[46] BC Cancer Agency provides a more general guideline for men with prostate cancer on ADT, in which DXA testing is recommended every 24 months, or 18 months if there are other risk factors for BMD loss.[47]

Another challenge is to determine an easily accessible form of intervention that could reduce or prevent ADT related fractures. Lifestyle modifications or pharmaceutical interventions are options, but it is not clear if these can prevent ADT related fractures. Lifestyle/behavioral modifications such as weight bearing and/or resistance exercises have been shown to maintain/increase BMD,[38,48,49] increase muscle strength,[50] and reduce the risk of fracture in older adults.[51-55] Lack of vitamin D and calcium intake are not uncommon in men with prostate cancer.[21, 56, 57] Vitamin D and calcium supplements are strongly considered for all men with prostate cancer having ADT. Bisphosphonates have shown to prevent ADT related bone loss in men with prostate cancer.[58-61] However, the routine use of bisphosphonates to prevent ADT induced bone loss or osteoporosis is not yet recommended.

Conclusion

Our findings suggest that prostate cancer per se does not increase the risk of fracture. However, Canadian men receiving ADT for their prostate cancer have significant increased risk of fracture and this risk persists for at least 1 year in past users. □

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