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ORIGINAL ARTICLE

Health care costs for prostate cancer patients receiving androgen deprivation therapy: treatment and adverse events

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ABSTRACT

Background

Serious adverse events have been associated with androgen deprivation therapy (ADT) for prostate cancer (PCa), but few studies address the costs of those events.

Methods

All PCa patients (ICD-9-CM 185) in Ontario who started 90 days or more of ADT or had orchiectomy at the age of 66 or older during 1995–2005 ($n = 26,809$) were identified using the Ontario Cancer Registry and drug and hospital data. Diagnosis dates of adverse events—myocardial infarction, acute coronary syndrome, congestive heart failure, stroke, deep vein thrombosis or pulmonary embolism, any diabetes, and fracture or osteoporosis—before and after ADT initiation were determined from administrative data. We excluded patients with the same diagnosis before and after ADT, and we allocated each patient's time from ADT initiation to death or December 31, 2007, into health states: ADT (no adverse event), ADT-AE (specified single adverse event), Multiple (>1 event), and Final (≤180 days before death). We used methods for Canadian health administrative data to estimate annual total health care costs during each state, and we examined monthly trends.

Results

Approximately 50% of 21,811 patients with no pre-ADT adverse event developed 1 or more events after ADT. The costliest adverse event state was stroke ($26,432/year). Multiple was the most frequent ($n = 2,336$) and the second most costly health state ($24,374/year). Costs were highest in the first month after diagnosis (from $1,714 for diabetes to $14,068 for myocardial infarction). Costs declined within 18 months, ranging from $784 per 30 days (diabetes) to $1,852 per 30 days (stroke). Adverse events increased the costs of ADT by 100% to 265%.

Conclusions

The economic burden of adverse events is relevant to programs and policies from clinic to government, and that burden merits consideration in the risks and benefits of ADT.

KEY WORDS

Prostatic neoplasms, androgen deprivation therapy, costs, adverse events, cost analysis

1. INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men in developed countries[1]. Many patients receive androgen deprivation therapy (ADT) as primary therapy for all stages of disease or in addition to primary surgery or radiotherapy[2–5]. Luteinizing hormone–releasing hormone (LHRH) agonists and anti-androgens are now the main types of ADT; bilateral orchiectomy and estrogen are less popular[5–7].

Recently, ADT has been viewed less favourably because of an awareness about its potential harms and its costs. Associated adverse events include hot flashes, sexual dysfunction, gynecomastia, increase in fat mass[8–10], and of greater concern, decline in bone mineral density, with a potential risk of fracture[11–13]. Also concerning is that ADT has been associated with a type of metabolic syndrome (increased cholesterol, triglycerides, and insulin resistance)[14], diabetes, and possibly myocardial infarction (MI) and sudden cardiac death[14–16]. Androgen deprivation therapy is costly: in 2013, one 3-month depot preparation of LHRH agonist cost approximately CA$1,100 in Ontario[17], and many patients are treated for years. Additional costs can be incurred to prevent or treat adverse events. One study reported an increase of $13,807 (2004 U.S. dollars) in 3-year ADT costs for fracture treatment[18].

The purpose of the present study was to estimate total health care costs in PCa patients receiving ADT in the province of Ontario, and to quantify the additional costs associated with the frequently-documented, serious, and potentially costly adverse events associated with ADT.

2. METHODS

2.1 Ethics

The study was approved by the Research Ethics Board of the University Health Network, Toronto, Ontario.

2.2 Patient Selection

From the Ontario Drug Benefit (ODB) program database (http://www.health.gov.on.ca/en/pro/programs/drugs/odbf_mn.aspx), we selected outpatient prescription records (n = 60,690) of men who began at least 90 consecutive days of LHRH agonist, estrogen, or antiandrogen from January 1, 1995, to December 31, 2005. The ODB program covers the costs of most outpatient prescriptions for Ontario residents 65 years of age and older. We specified 90 days because it is the recommended minimum therapeutic period of ADT given for any indication[19]. Following standard practice, we allowed patients up to 50% of the number of days of drug supplied to refill the prescription[20]. Thus, a patient had up to 45 days to refill a prescription for a 30-day depot injection of an LHRH agonist or to obtain a new ADT prescription.

We combined the foregoing patient records with the records of patients who underwent bilateral orchiectomy as recorded in health care administrative databases during 1995–2005 (n = 13,561). We combined all records for each patient to obtain a cohort of 52,855 unique ADT recipients who received pharmacologic ADT, surgical ADT, or both. We defined each patient's index date as the first date of any ADT.

We linked those patients to the Ontario Cancer Registry[21] and included all patients with an initial diagnosis of PCa (International Classification of Diseases code ICD-9-CM 185), but no other primary cancer, before or within 6 months after their ADT index date (n = 33,141). We excluded patients less than 66 years of age at the index date so that prescription drug data for a full year were available to assess prior ADT. Other exclusion criteria were sex coded as female or missing, non-Ontario residence, invalid or missing Ontario Health Insurance Plan (OHIP) number, missing histology code in the Ontario Cancer Registry, and death within 90 days after the index date. After those exclusions, 29,554 patients remained. Using the ODB program database, we then identified and excluded patients who had received any pharmacologic ADT before January 1, 1995, and before age 66, and using hospital records, we excluded those who had undergone orchiectomy before January 1, 1995, and as far back as 1988 (n = 2745).

The final cohort numbered 26,809. After determining pre- and post-ADT adverse events, we excluded patients who experienced the same adverse event before and after ADT, leaving 21,811 patients for the subsequent analyses. We followed patients from the start of ADT until death or until December 31, 2007.

2.3 Data and Costing

All medically necessary health care for permanent residents of Ontario is covered under OHIP (http://www.health.gov.on.ca/en/public/programs/ohip). We identified and costed all resources used by each patient and paid by OHIP from the patient's index date (start of ADT) until death or December 31, 2007. Most data were available at the Institute for Clinical Evaluative Sciences, Toronto, Ontario. Radiation therapy and New Drug Funding Program data were obtained from Cancer Care Ontario. Data were linked using the patient's unique OHIP number and anonymized.

Hospital admissions were determined using the Discharge Abstract Database from the Canadian Institute for Health Information (http://www.cihi.ca/cihi-ext-portal/internet/en/document/types+of+care/hospital+care/acute+care/dad_metadata). Outpatient visits, including those to regional cancer centres, were determined using the National Ambulatory Care Reporting System from the Canadian Institute for Health Information (http://www.cihi.ca/CIHI-ext-portal/internet/en/document/types+of+care/hospital+care/emergency+care/NACRS_METADATA). Every record is assigned a resource intensity weight associated with its case-mix group (developed by the Canadian Institute for Health Information[22]). Using standard costing procedures, we estimated costs by multiplying the resource intensity weight by the cost per weighted case in Ontario for the year of use[22,23]. We included cancer drugs and costs recorded in the New Drug Funding Program (https://www.cancercare.on.ca/toolbox/drugs/ndfp). That program reimburses cancer centres and hospitals for expensive chemotherapy approved for specific cancers. Costs for pharmacologic ADT and other outpatient prescription medications were identified from the ODB program database.

We used the OHIP Claims History database to identify costs for inpatient and outpatient physician services and outpatient diagnostic tests. Data from the Radiation Oncology Research Unit database were used to identify curative and palliative radiation therapy. In Ontario, many radiation oncologists receive all or a portion of their income through alternative funding plans[24]. We estimated that income (in addition to OHIP claims) from responses on the 2004 and 2007 National Physician surveys (http://nationalphysiciansurvey.ca/).

We used the Home Care Database and Ontario Home Care Administrative System data to identify home care services, and we obtained average service costs from Community Care Access Centres in Toronto (http://healthcareathome.ca/).

We included stays at complex continuing care facilities. Each stay is assigned a case-mix index indicating the intensity of the required care. We multiplied that index by the length of stay and the provincial average cost per weighted chronic day for the year of stay.

All costs were adjusted to 2009 Canadian dollars using the Consumer Price Index for health[23,25,26]. We summed all resource costs for each patient to estimate total health care costs.

2.4 Comorbidity and Demographics

We described comorbid illness by categorizing all of the ICD-9 or ICD-9-CM and ICD10 diagnostic codes in hospital records and physicians' billings data in the year before each patient's index date into one of nearly 90 adjusted clinical groups, a population–patient case-mix adjustment system[27]. Being interested in the burden of comorbidity, we classified patients into groups of 0–3, 4–6, 7–9, or 10+ adjusted clinical groups, representing low, moderate, high, and very high comorbidity respectively[27].

We used the Statistics Canada Postal Code Conversion file and data from the 2001 Canadian census to assign patient postal codes to standard geographic areas, for which data on neighbourhood-level median household income quintiles and rurality were obtained.

2.5 Adverse Events and Health States

We used diagnosis codes in several of the administrative databases to identify the following serious adverse events that have been associated with ADT in the literature: MI, acute coronary syndrome (ACS), congestive heart failure (CHF), stroke, deep vein thrombosis or pulmonary embolism, diabetes (any type), and fracture or osteoporosis[15]. We determined the diagnosis dates of those events in the 3 years before each patient's index date (before ADT) and any time after each patient's index date to December 31, 2007, or date of death (after ADT). Patients could experience more than 1 adverse event in each time period.

After excluding patients who had experienced the same event before and after ADT, we divided each patient's post-ADT observation time into mutually-exclusive health states, similar to those used in health-state transition models (Markov models)[28]. Such models characterize the course of a disease, with transitions between health states. A single patient moves from one health state to another, but can be in only one health state at any given time. The three major health states in our study were ADT (no adverse events), ADT-AE (diagnosis of an adverse event), and Final (date of death and up to 180 days before the date of death).

The ADT health state represented time on ADT with no adverse events, and before 180 days before death. When and if an adverse event was diagnosed, patients entered the ADT-AE state, which was labelled according to the adverse event: MI, ACS, CHF, stroke, deep vein thrombosis or pulmonary embolism, diabetes, or fracture or osteoporosis. When patients experienced a different adverse event, they entered the Multiple state on the first day of the second type of adverse event. As a hypothetical example, consider a patient who did not die during the study observation period; whose ADT index date was March 1, 2000; who was diagnosed with diabetes on December 1, 2000; and who then experienced a MI on June 1, 2001. His sequence of health states would be: ADT from March 1, 2000, to November 30, 2000; MI from December 1, 2000, to May 31, 2001; and Multiple from June 1, 2001, to December 31, 2007.

Patients who did not die and experienced no adverse events were in the ADT state for all of their observation time. Patients who died were in the Final state for the 180 days before death (but not extending before the start of ADT). The Final state superseded all other states. For example, if the hypothetical patient in the earlier example had died on November 30, 2003, his Multiple state would have ended on June 2, 2003, and he would have been in the Final state from June 3, 2003, to November 30, 2003.

A patient who died within 180 days after his index date spent all of his observation time in the Final state. Because patients might have died within 180 days after December 31, 2007, we looked forward 179 days from December 31, 2007, to check for a date of death. All days between the death date minus 180 days and December 31, 2007, were assigned to the Final state.

2.6 Statistical Methods

We described patient characteristics using means and standard deviations for continuous variables and frequency counts for categorical variables. We counted the number of patients who experienced each adverse event before and after the start of ADT and expressed it as a rate per 100 patient–years to account for the longer post-ADT period. Based on Poisson distribution, we calculated 95% confidence intervals for the rates; confidence intervals that do not overlap are statistically significant[29]. After selecting patients with newly-diagnosed post-ADT adverse effects and allocating their time into states, we calculated the number of patients with time in each state and the state durations. To describe progression through the states, we examined the cohort cross-sectionally at 1 year, 3 years, and 5 years after the start of ADT and determined the number of patients in each health state.

We estimated total health care costs during each patient's observation time, as earlier described, and we then computed the total costs for all resources incurred by each patient during the time spent in each health state. Because each patient spent a variable amount of time in each state, we reported costs per state standardized to 1 year. Within each state, mean cost per year was computed as follows:

Mean cost per year =
(total costs for all patients /
number of person–days) × 365.25.

The result was halved for the 6-month Final state. We computed annual costs per state (6-month costs for the Final state) for all patients, for two age groups (66–74 years and 75+ years at the start of the state), and for three comorbidity groups (0–6, 7–9, or 10+ adjusted clinical groups at the patient's index date). Most of the adverse effects would require intense intervention immediately after diagnosis, with less-intense follow-up. We examined the mean cost in the first 30 days and the mean cost in the remainder of each health state separately.

To estimate time trends, we computed mean total costs for each 30-day period from the first day of each health state to the maximum length of the state. The total cost for all patients who had any time in each 30-day period was divided by the number of patients with time in those 30 days until the maximum length of the state was reached and no patients remained.

All analyses were conducted using the SAS statistical software (version 9.1.3: SAS Institute, Cary, NC, U.S.A.).

3. RESULTS

Table I describes the characteristics of the initial cohort of 26,809 patients and of our selected cohort of 21,811 who did not experience the same adverse event before and after ADT. The mean age of the 21,811 patients was 75.4 years, and 56% were 70–79 years of age. Approximately 60% were diagnosed during 1990–1999, and 41% were diagnosed during 2000–2005. By December 31, 2007, 54% of the patients were alive. The 21,811 patients who had experienced new post-ADT adverse events had more comorbidities than the entire cohort of 26,809 patients because the adverse events contributed to comorbidity.

Table II shows how many of the 26,809 patients experienced each event before and after the start of ADT. Diabetes was the most common condition in both time periods, diagnosed in 3574 patients before ADT and in 5614 after. The incidence of fracture or osteoporosis—diagnosed in 1199 patients before ADT (rate: 1.49 per 100 patient–years) and in 4508 after ADT (rate: 3.32 per 100 patient–years)—increased more than any other adverse event. The diagnosis rate of the least-frequent adverse event, ACS, showed no significant increase after ADT.

Table III shows the allocation of observation time to health states (after exclusion of patients who had the same adverse event before and after ADT). Almost all patients (98%) had time in the ADT state. Approximately

TABLE I Characteristics of the patient cohort at the index date

Characteristic	*Patients*			
	Overall (N = 26,809)		*With a new post-ADT adverse event (N = 21,811)*	
	(n)	*(%)*	*(n)*	*(%)*
Age (years)				
Mean	75.5±6.1		75.4±6.1	
Median	75		75	
IQR[a]	71, 80		71, 79	
Age group				
66–69 Years	4,978	18.6	4,176	19.1
70–74 Years	7,792	29.1	6,376	29.1
75–79 Years	7,333	27.3	5,958	27.2
80–84 Years	4,415	16.5	3,539	16.2
≥85 Years	2,291	8.5	1,832	8.4
Comorbidity (*n* ACGs)				
0–3	3,196	11.9	1,167	5.3
4–6	10,978	40.9	5,649	25.8
7–9	8,468	31.6	7,803	35.7
10+	4,172	15.6	7,262	33.2
Diagnosis year				
1965–1969	6	0.02	5	0.02
1970–1979	101	0.4	80	0.4
1980–1989	921	3.4	751	3.4
1990–1999	14,872	55.5	12,161	55.6
2000–2005	10,909	40.7	8,884	40.6
Status at Dec 31, 2007				
Alive	13,945	52.0	11,782	53.8
Dead	12,864	48.0	10,099	46.15
Neighbourhood income quintile				
1 (lowest)	4,769	17.8	3,781	17.3
2	5,532	20.6	4,465	20.4
3	5,428	20.3	4,449	20.3
4	5,232	19.5	4,304	19.7
5 (highest)	5,784	21.6	4,837	22.1
Missing	64	0.2	45	0.2
Rurality[b]				
Urban	21,872	81.6	17,805	81.4
Rural	4,926	18.4	4,070	18.6
Missing	11	0.04	6	0.03

[a] 25th, 75th percentile.
[b] Communities with a population of less than 10,000 were defined as rural.

ADT = androgen deprivation therapy; IQR = interquartile range; ACG = adjusted clinical group.

TABLE II Number of patients experiencing each adverse event before and after initiation of androgen deprivation therapy (ADT)

Adverse event			*Proportion of cohort (% of 26,809)*	*Per 100 patient–years*	
Type	*Timing*	*(*n*)*		*Rate*	*95% CI*
Myocardial infarction	Before ADT	956	3.57	1.19	1.11 to 1.26
	After ADT	2,511	9.37	1.85	1.78 to 1.92[a]
Acute coronary syndrome	Before ADT	402	1.50	0.49	0.44 to 0.54
	After ADT	586	2.19	0.43	0.39 to 0.46
Congestive heart failure	Before ADT	1,575	5.87	1.96	1.86 to 2.06
	After ADT	4,589	17.12	3.68	3.58 to 3.78[a]
Stroke	Before ADT	1,130	4.22	1.40	1.32 to 1.48
	After ADT	3,237	12.07	2.38	2.30 to 2.46[a]
Deep vein thrombosis or pulmonary embolism	Before ADT	571	2.13	0.71	0.65 to 0.77
	After ADT	1,620	6.04	1.19	1.13 to 1.25[a]
Diabetes	Before ADT	3,574	13.33	4.44	4.29 to 4.59
	After ADT	5,614	20.94	4.13	4.02 to 4.24
Fracture or osteoporosis	Before ADT	1,199	4.47	1.49	1.41 to 1.57
	After ADT	4,508	16.82	3.32	3.22 to 3.42[a]

[a] Statistically significant difference from rate before ADT ($p < 0.05$)
CI = confidence interval.

37% of patients ($n = 8095$) spent time in at least one adverse event state. Diabetes was the most common and longest adverse event state ($n = 1775$; mean duration: 1120 days). Many patients experienced more than one adverse event, and 2336 patients spent time in the Multiple state. The shortest state, CHF, had a mean length of 753 days. Thus, many patients died or developed another adverse event after CHF.

Figure 1 shows the proportion of patients in each health state at 1, 3, and 5 years after their index date, excluding patients who died (7%, 30%, and 50% of the entire cohort at 1, 3, and 5 years respectively). After 1 year of ADT, only 9.5% of the surviving patients were in an adverse event health state. Over time, the percentage of patients in ADT decreased, and patients moved into adverse event states and died. The most common adverse event states 5 years after ADT initiation were diabetes and stroke.

3.1 Costs per Health State

Overall, the least costly health state was ADT. The mean cost per year was $9,959 (Table III). Adverse events (except for diabetes) increased the cost of ADT by approximately 150% (ACS and deep vein thrombosis) to 265% (stroke), over the length of the entire state. The most costly adverse event state was stroke ($26,432 annually); diabetes was the least costly ($9,850 annually). The most costly health state was Final. The mean cost for the 6-month period before death was $26,091, a 524% increase over the cost for the ADT state.

Costs for all health states except Final increased with age (Table III). The mean cost in the 6-month Final state was $28,666 for patients 66–74 years of age and $24,520 for older patients, likely reflecting less-intense end-of-life interventions for the oldest patients. Changes in costs across comorbidity strata were smaller and less consistent. For example, mean MI costs were $17,179 and $19,249 per year for patients with a low and high burden of comorbidity respectively.

3.2 Trends in Costs

Figure 2 shows the mean cost in the first 30 days of each health state and the mean cost in the remaining time. The first 30 days of the ADT state cost approximately 4.5 times the mean cost per 30 days for the remainder of the state. The mean cost in the first 30 days of the MI and ACS states was, respectively, 15 and 11 times that of the subsequent mean 30-day cost. However, the 30-day cost for the Final state increased as death approached.

After the first 30 days, the mean cost per 30-day period in the ADT and adverse event states gradually declined until stabilizing at approximately 12 months. Figure 3 shows, for ADT and for 4 representative adverse event phases (stroke, osteoporosis or fracture, diabetes, and Multiple) the mean cost for each 30 days after ADT initiation, from the 2nd to the 60th period (5 years). By 5 years, 10%–23% of the patients who had started each state were still in that state. To facilitate observation of trends, the data have been smoothed[a]. Patients with stroke and with fracture or osteoporosis incurred high costs for approximately 1 year after onset. Diabetes

[a] Cucka J. A macro for efficient and flexible data smoothing. Presented at the Midwest SAS User Group Conference; Chicago, IL, U.S.A.; September 28–30, 1997. [Available online at: http://www2.sas.com/proceedings/sugi22/CODERS/PAPER85.PDF; cited October 15, 2013]

TABLE III Summary of each health state for all patients with a new adverse event after androgen deprivation therapy (ADT)

Variable	*Health state*									
	ADT	*Acute coronary syndrome*	*Congestive heart failure*	*Deep-vein thrombosis or pulmonary embolism*	*Myocardial infarction*	*Diabetes*	*Fracture or osteoporosis*	*Stroke*	*Multiple events*	*Final*[a]
All patients (*n*)	21,394	183	1,327	596	716	1,775	2,162	1,109	2,336	10,624
Health state length (days)										
Mean	1390	997	753	1010	769	1121	922	893	954	174
Median	1138	559	539	636	499	893	726	618	717	180
Range	1–4743	1–3708	1–4263	1–4618	1–4260	1–4725	1–4529	1–4319	1–4283	1–180
Mean annual cost[b]	$9,959	$14,354	$16,899	$14,647	$17,094	$9,850	$20,503	$26,432	$24,374	$26,091
Increase from ADT[c]		144%	170%	147%	172%	99%	206%	265%	245%	524%
Age group										
66–74 Years (*n*)	10,416	92	486	317	342	1,041	1,006	453	1,050	4,017
Mean annual cost[b]	$8,571	$13,478	$14,050	$11,201	$15,316	$8,656	$12,565	$22,353	$21,720	$28,666
≥75 Years (*n*)	10,978	91	841	279	374	734	1,156	656	1,286	6,607
Mean annual cost[b]	$11,737	$15,560	$19,005	$19,857	$19,322	$11,980	$21,769	$29,756	$27,029	$24,520
Comorbidity										
0–6 ACGs (*n*)	6,720	51	289	167	209	620	606	288	570	2,917
Mean annual cost[b]	$8,462	$16,899	$14,561	$14,147	$17,179	$9,168	$14,452	$25,068	$23,717	$25,446
7–9 ACGs (*n*)	7,636	53	463	219	275	633	769	414	852	3,678
Mean annual cost[b]	$9,655	$13,965	$15,170	$12,979	$15,134	$9,472	$17,398	$25,324	$21,952	$25,994
≥10 ACGs (*n*)	7,038	79	575	210	232	522	787	407	914	4,029
Mean annual cost[b]	$12,090	$13,161	$19,736	$16,832	$19,249	$11,213	$18,226	$28,538	$27,114	$26,657

[a] Final health state costs are for 6 months, the maximum length of the Final health state.
[b] 2009 Canadian dollars.
[c] Percentages have been rounded.
ACG = adjusted clinical group.

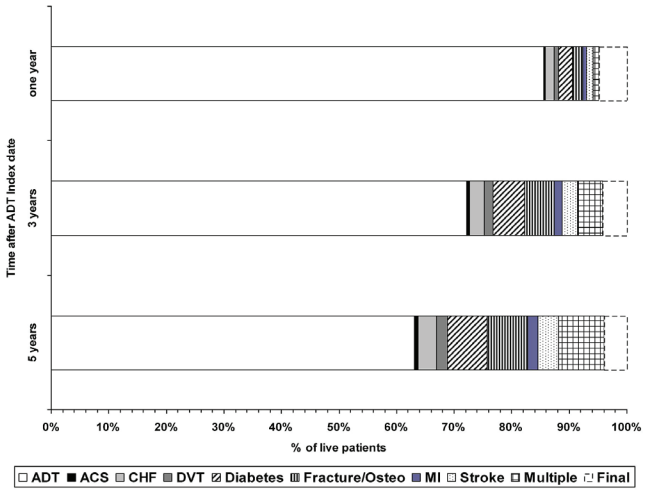

FIGURE 1 Distribution of surviving patients among health states at 1 year, 3 years, and 5 years after the start of androgen deprivation therapy (ADT). ACS = acute coronary syndrome; CHF = congestive heart failure; DVT = deep vein thrombosis or pulmonary embolism; Osteo = osteoporosis; MI = myocardial infarction.

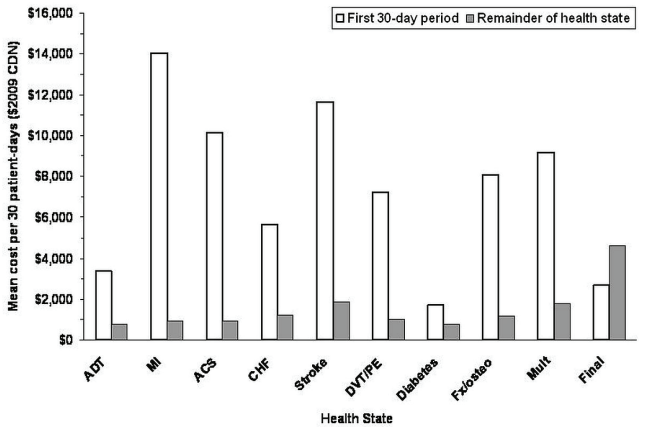

FIGURE 2 Mean health state costs per 30 patients–days in the first 30-day period and in the remainder of each state. CDN = Canadian; ADT = androgen deprivation therapy; MI = myocardial infarction; ACS = acute coronary syndrome; CHF = congestive heart failure; DVT/PE = deep vein thrombosis or pulmonary embolism; Fx/osteo = fracture or osteoporosis; Mult = multiple events.

had the lowest cost of all adverse events. The Multiple state had the highest cost over most of the follow-up time, because it included the costs of 2 or more adverse events (Figure 3).

Patients in the Final state incurred higher costs as death approached (data not shown). Mean cost per patient steadily increased from $2,655 in the 6th month before death to $7,616 in the 30 days before death.

4. DISCUSSION

This study, like others, showed that adverse events are common after receiving ADT. Approximately 50% of our cohort of PCa patients treated with at least 90

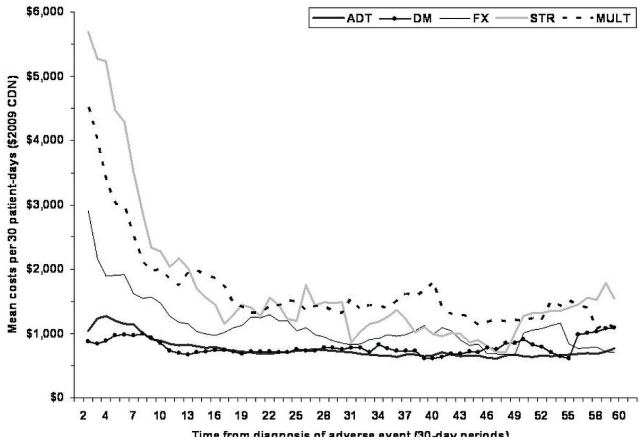

FIGURE 3 Mean costs for androgen deprivation therapy (ADT) and selected representative adverse event health states per 30 days for the first 5 years after the first 30 days. CDN = Canadian; DM = diabetes mellitus; FX = fracture; STR = stroke; MULT = multiple events. Data have been smoothed for plotting the graph[30].

days of ADT developed one or more of the adverse events that have been documented as potential side effects. We also showed that the cost of care for individuals who experience one of those adverse events is very substantial. Our study makes the unique contribution of quantifying those economic costs. After the occurrence of adverse events, total health care costs ranged from 99% (diabetes) to 524% (multiple events) of baseline ADT costs.

Our study is, to our knowledge, the only one to have examined the health care costs associated with 7 adverse events (and their combinations) that have been documented as side effects of ADT. Other studies have examined the overall cost of care in patients receiving ADT[30–34] or the cost of treating or preventing fragility fractures in this population[18,35]. Other strengths of our study include the use of a large population-based sample of all PCa patients 66 years of age and older who received ADT in a large Canadian province. Our costing approach was comprehensive: the data included all records of the costed resources, and the public health care system covered almost all of the direct costs. In contrast, in the United States, the costs would have been borne by some combination of public insurance (for example, Medicare), private insurance, and the patients themselves. Costs that we did not consider include patient-borne indirect costs for travel and time associated with obtaining health care, which would likely to be higher among patients with adverse effects. We did not examine use of, or costs for, over-the-counter drugs or complementary and alternative medicine, which are not covered by OHIP.

We defined a Final state because other studies have shown that end-of-life is an extremely costly period[36,37]. Extending the ADT and adverse event states until death would greatly increase the overall

costs of ADT and the adverse events. However, adverse events that occurred within 6 months before death are not identified in our study.

Our study design did not allow inference about causality. We cannot estimate with confidence the rate at which complications increased because of ADT therapy. However, we can say how much the adverse effects cost. We provide accurate estimates of the total cost profiles for PCa patients who experienced adverse events that have been documented to be common ADT complications, including trends in costs over short time periods and across age and comorbidity strata. We believe that our estimates of the costs associated with adverse effects, in conjunction with estimates of attributable risk drawn from other published studies, will be invaluable in predicting the health and economic consequences of alternative ADT strategies for PCa. In particular, such costs are extremely useful for informing pharmacoeconomic and cost-effectiveness models, which are typically state-transition models. They incorporate health states, such as those defined in our study, representing the disease, disease treatment, and treatment outcomes. Our study provides valid and robust estimates of the total cost of health care associated with ADT and its most common adverse effects.

5. CONCLUSIONS

Our analysis found that adverse events increased the cost of ADT by up to 500% and thus added a considerable economic burden to the care of patients receiving ADT. Clinical practice guidelines and reimbursement recommendations should consider the health care costs related to adverse events in the risk–benefit calculation of ADT. Our methods can be applied to cohorts of patients who have received new types of ADT, including abiraterone and enzalutamide for metastatic castration-resistant PCa[38,39], when long-term data are available. To understand the additional total costs associated with ADT care, comprehensive analyses matching similar patients who did and did not receive ADT should be conducted.

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7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest.

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