Health Care Costs for State Transition Models in Prostate Cancer

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Objective. *To obtain estimates of direct health care costs for prostate cancer (PC) from diagnosis to death to inform state transition models.* ***Methods***. *A stratified random sample of PC patients residing in 3 geographically diverse regions of Ontario, Canada, and diagnosed in 1993–1994, 1997–1998, and 2001–2002, was selected from the Ontario Cancer Registry. We retrieved patients' pathology reports to identify referring physicians and contacted surviving patients and next of kin of deceased patients for informed consent. We reviewed clinic charts to obtain data required to allocate each patient's observation time to 11 PC-specific health states. We linked these data to health care administrative databases to calculate resource use and costs (Canadian dollars, 2008) per health state. A multivariable mixed-effects model determined predictors of costs.* ***Results***. *The final sample numbered 829 patients. In the regression model, total direct costs increased with age, comorbidity, and Gleason score (all P < 0.0001). Radical prostatectomy was the most costly primary treatment health state ($4676 per 100 days). Radical prostatectomy, hormone-refractory metastatic disease ($6398 per 100 days), and final (predeath) ($13,739 per 100 days) health states were significantly more costly (P < 0.05) than nontreated nonmetastatic PC ($3440 per 100 days), whereas the postprostatectomy ($732 per 100 days) and postradiation ($1556 per 100 days) states cost significantly less (P < 0.0001).* ***Conclusions***. *This study used an innovative but labor-intensive approach linking chart and administrative data to estimate health care costs. Researchers should weigh the potential benefits of this method against what is involved in implementation. Modifications in methodology may achieve similar gains with less outlay in individual studies. However, we believe that this is a promising approach for researchers wishing to advance the quality of costing in state transition modeling.* ***Key words:*** *prostate cancer; costs; economic evaluation.* ***(Med Decis Making 2014;34:366–378)***

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Prostate cancer (PC) is the most common cancer among men in Canada, the United States, and Europe and one of the most common causes of cancer death.[1] In addition to premature death and morbidity, PC exacts an enormous economic burden from initial care[2,3] to the end of life.[4–6] For example, mean prostate-specific costs ($2004) for the first year after diagnosis were estimated as $CAN 8636 in Canada[4] and $10,612[5] and $13,091[2] in the United States.

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Cost-effectiveness analysis is used to evaluate the costs and consequences of health programs or treatments.[7] Unfortunately, the evidence characterizing resource use and costs is often of low quality. For example, many costs are derived from the literature[8] or a single institution[9] and are not well described.[10] In particular, utilization estimates, an important component of costs, are often not well characterized.

Cost-effectiveness analyses often use health state transition models (Markov models). Such models characterize a health condition using a set of mutually exclusive health states, linked to an underlying biologic model of disease. The course of disease is characterized by transitions between health states.[11] Because this type of model represents temporal events, it can accommodate the long time horizon of PC. State transition models have been used widely in PC.[12–14]

When the outcome of a state transition model includes cost (e.g., cost per life year, cost per quality-adjusted life year), a cost is required for each health state in the model. Administrative data, such as the linked Surveillance, Epidemiology and End Results (SEER)–Medicare database, provide cost estimates for large, representative groups of patients over long periods[5,15] and are an excellent source of utilization and costing data.[16] They are ideal for estimating long-term costs because patients can be followed for many years.

Administrative data can be used to construct longitudinal cost profiles in several ways. One approach is ''phases of care,'' in which the time from diagnosis to death is divided into ''phases'' representing the clinical course of disease.[15] The phases are based on only 2 events: date of diagnosis and date of death. For example, the first few months after diagnosis are ''initial care,'' typically a period of high costs for primary and adjuvant treatment. A period, such as 6 months, before the date of death is the ''terminal care'' phase. The time between is ''continuing care.''[15] However, a major limitation of these phases of care derived from administrative data is that they lack enough clinical detail to define health states in state transition models. For example, health states in PC models are often characterized by prostate-specific antigen (PSA) levels, tumor grade, tumor stage at diagnosis, and disease progression. Therefore, the costs of phases of care are not suitable for use in state transition models.

This study describes an alternative method of constructing longitudinal cost profiles that can be used in health state transition models. This method uses both detailed chart abstraction and administrative data to estimate costs for health states from diagnosis to death, using the example of PC.

OBJECTIVE

The objective of this study was to obtain high-quality estimates of direct health care costs in PC patients for health states included in state transition models, using a population-derived sample, clinical chart review, and administrative records. This work is part of a research program evaluating costs and quality of life in PC.

METHODS

Ethics

This study was approved by the Research Ethics Boards of the University Health Network and the University of Toronto. All surviving participants provided written informed consent. We attempted to contact the next of kin of deceased patients to obtain written consent. The charts of deceased patients were reviewed after several unsuccessful attempts to contact any family members.

Patient Recruitment

Patients were identified from the Ontario Cancer Registry (OCR),[17] the population-based registry for Canada's largest province, maintained by Cancer Care Ontario (www.cancercare.on.ca). We selected patients with an initial diagnosis of PC in 1993–1994, 1997–1998, and 2001–2 and residing in 3 counties: Toronto and York Region, which represent large urban and suburban areas in southern Ontario, respectively, and Sudbury, a city in northern Ontario.

Patients were excluded if they had matching diagnosis and death dates, missing histology codes, billing or hospitalization diagnosis codes of PC prior to the OCR diagnosis date, prior prostatectomy (any type), sex coded female or missing, non-Ontario residence, or missing Ontario Health Insurance number.

We included all patients from York Region (approximately 200 per year) and Sudbury (approximately 100 per year) and a random selection of 200 per year from Toronto, where approximately 1300 patients were diagnosed per year. Paper pathology records were retrieved and the contact information of the referring physician was obtained from the College of Physicians and Surgeons of Ontario (http://www.cpso.on.ca/). Physicians were mailed a list of their patients and personalized patient letters introducing the study. Physicians were asked to sign the letters, indicating their permission to allow us to

contact their patients. If the patient had died, we prepared a letter to his next of kin (identified by the physician's office) requesting consent to review the patient's chart. Physicians returned the signed letters and contact information of the patients or next of kin and we mailed the letters.

The letters described the study purpose, the chart review, the linkage to health care administrative databases, and a quality-of-life survey (results to be reported elsewhere). Next of kin were told about the chart review and data linkage. Local and toll-free telephone numbers and an e-mail address were provided for replies. We telephoned if we had not received a reply 10 days after the letters were mailed.

Three chart abstractors traveled to physicians' offices and hospitals in each region to review medical charts. Information collected included tumor grade (Gleason score) and stage (TNM staging) at diagnosis, all treatments for PC and their dates, and all PSA levels and their dates from diagnosis onwards. We reviewed the physicians' notes and recorded evidence of biochemical recurrence, clinical recurrence, or metastases and their dates. The results of diagnostic tests and scans were also reviewed for evidence of cancer progression or metastases. Data were collected on a laptop computer using commercial database software or on paper forms with subsequent computer entry.

Patient recruitment began in January 2004. Chart reviews were completed between May 2004 and December 2006.

Data Collection

A database programmer and the study coordinator used the chart review database to allocate each patient's observation time into discrete health states, using predefined criteria (see ''Defining Health States'' below). The health state periods and other data from the chart reviews were sent to the Institute for Clinical Evaluative Sciences (ICES; http://www.ices.on.ca) for deterministic linkage to health care administrative databases using Ontario Health Insurance Plan numbers. Data on health care resource use during each health state were obtained for each patient and costs assigned to each resource, as described in ''Costing Methodology.''

Defining Health States

We constructed a state-transition model that included a set of mutually exclusive PC health states and allowable transitions between them.[18] We based our model on published decision analyses,[13,14,19] literature review, and discussions with local content experts. Our model had 11 health states: nontreated nonmetastatic PC, radical prostatectomy (RP), radiation therapy (RT), hormone treatment (HT) for nonmetastatic PC, post-RP, post-RT, recurrence/progression, HT-refractory recurrence/progression nonmetastatic PC, metastatic PC stable, refractory/progression metastatic PC, and final (the 6 months prior to death).

The index date was the date of PC diagnosis. Nontreated nonmetastatic PC was the time between diagnosis and the start of any other health state. This is the time immediately following diagnosis when no treatment is being given, when further diagnostic tests such as scans may be done, and when treatment decisions may be made. Some patients in this state may be managed with watchful waiting or active surveillance.[20] The RP and RT health states included up to 182 days before the start of treatment and 1 year after treatment to include costs related to treatment planning and preparation, as well as posttreatment procedures. Post-RP and post-RT were stable periods following treatment. The RP, RT, and final states had maximum observation times (18 months, 18 months, and 6 months, respectively); other health states had no maximum. We did not set a minimum duration for any health state. Patients moved into a health state when they met its criteria. Supplemental Appendix 1 describes the criteria for the health states and allowable transitions between them.

Some examples of trajectories that we observed in the data illustrate the typical course of PC. For example, one scenario would be a patient who entered the model with nontreated nonmetastatic PC (Appendix 1), was treated with hormone therapy (hormone-treated localized PC), developed metastases (metastatic PC stable), progressed while on HT (HT refractory/progression metastatic PC), and died (final). A patient who decided on RP immediately following diagnosis and had surgery a few months later might enter the model at RP and then transition to post-RP. He would remain in that health state for the remainder of his observation time unless he had recurrence or progression or died of another cause. RP patients who did transition to ''recurrence/progression'' could potentially progress to the metastatic health state or final. Patients who were diagnosed with metastatic PC could move to only 2 other health states: refractory/progression metastatic PC and/or final (Appendix 1).

The final health state was allocated before any other health state in patients who died. Any evidence of progression or metastases that was first detected

within 6 months of death was incorporated into the final health state.

Costing Methodology

Under the Canada Health Act,[21] all residents of Canada are eligible for universal government-sponsored health care insurance coverage; plans are managed by the provinces and territories. Residents of Ontario are eligible for coverage for medical services paid for by the Ontario Ministry of Health and Long-Term Care under the Ontario Health Insurance Plan (OHIP; http://www.health.gov.on.ca/en/public/programs/ohip/).

We identified and costed all health-related resources used by patients and paid for by the Ontario Ministry of Health and Long-Term Care, using health care administrative data held at ICES. Our costing methods followed guidelines established by the Canadian Agency for Drugs and Technology in Health[22] and have been used in other economic studies.[4,23] We used the health care component of the Statistics Canada Consumer Price Index for Ontario (www.statcan.ca) to adjust all costs to 2008 Canadian dollars ($CAD) when 2008 costs were not available.

The resources and source databases are described in detail in Supplemental Appendix 2 and included outpatient diagnostic tests, emergency room visits, and physician services (Claims History Database of the Ontario Health Insurance Plan); hospital admissions and same-day surgery (Canadian Institute for Health Information-Discharge Abstract Database; www.cihi.ca); outpatient prescription drugs and length of stay in long-term care facilities (Ontario Drug Benefit Plan database; www.health.gov.on.ca/english/public/program/drugs/drugs_mn.html); stays in complex continuing care facilities (Complex Continuing Care database); home care services (Ontario Home Care Administrative System database); and radiation therapy (Radiation Oncology Research Unit database, housed at Queen's University, Kingston, Ontario).

Measuring Comorbidity and Socioeconomic Status

We used the Johns Hopkins Adjusted Clinical Groups System to categorize all of the *International Classification of Diseases, Ninth Revision* (*ICD-9*)/*ICD-9, Clinical Modification* (*ICD-9-CM*) and *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnostic codes in hospital records and physicians' billings data from 1 year before each patient's diagnosis and before the start of each health state into 32 ambulatory diagnostic groups (ADGs). The number of ADGs assigned to an individual serves as a robust measure of comorbidity.[24–26] We categorized the total number of ADGs per patient into 10 (high), 6 to 9, 3 to 5, 1-2 (low), and 0 (no utilization).[24,26]

We used the Statistics Canada Postal Code Conversion file and 2001 Canadian census data to determine neighborhood income equivalent (socioeconomic status measured in quintiles) and the Rurality Index for Ontario (RIO)[27] for each patient. The latter measures population and geographic factors related to the presence and availability of health services.

Data Analysis

We calculated resource use and costs during each health state, standardized to costs per 100 patient-days to control for varying amounts of time in each health state. We observed unexpectedly high average costs during the nontreated nonmetastatic PC health state. Further analyses revealed that the highest costs were from a group of older patients (24% aged 80 years and older), with high comorbidity, diagnosed in hospital, with tumor stage T1, T1A, or T1B at diagnosis,[28] whose initial pathologic diagnosis was secondary to a transurethral resection of the prostate, cystectomy, or cystoprostatectomy specimen. Few received curative treatment for their low-grade PC, likely due to their age and/or comorbidity. These patients did not represent the typical patients diagnosed with PC in recent years or meet the suggested criteria for either active surveillance or watchful waiting.[29] Because their costs would not be representative of patients in PC decision models characterizing early treatment decisions, we excluded patients with 1 or more of the following characteristics: 1) tumor stage T1, T1A, or T1B at diagnosis; 2) initial pathologic diagnosis was from a transurethral resection of the prostate, cystectomy, or cystoprostatectomy specimen; and 3) in hospital on the first day of their initial health state.

To validate our cost estimates and health states, we compared the costs derived from this study with those from a previous study.[4] That study used only administrative health data and allocated each patient's observation time to 5 chronologically defined phases of care linked to 2 index dates, diagnosis and death.[15] Phase I (prediagnosis) was the period 6 months before diagnosis and has no equivalent in the current study. Phase II (initial care) was the first 12 months after diagnosis. Phase V (final) was

assigned to patients who died and covered the 6 months before death. Phase IV (prefinal) was the 12-month period prior to phase V. Phase III (continuing care) covered all remaining observation time after phase II and before phase IV. We grouped our 11 health states into phases II to V (phase I is prediagnosis and has no equivalent in the present study) as follows: nontreated nonmetastatic PC, RP, RT, and HT for nonmetastatic PC into phase II (initial care); post-RP, post-RT, and recurrence/progression into phase III (continuing care); HT-refractory recurrence/progression nonmetastatic PC, metastatic PC stable, and refractory/progression metastatic PC into phase IV (prefinal); and final into phase V. We compared the average costs per 100 patient-days during each phase with the average costs per 100 patient-days in each of the health states that corresponded to it.

We used a mixed-model multivariable regression with random intercepts to determine predictors of costs. Random intercepts were used to account for the nonindependence of the observations, due to patients with multiple health states. The dependent variable was natural log-transformed total cost per 100 days. The value ''1'' was added to total cost before transformation to ensure that zero costs would be included. We used multiple imputation (SAS version 9.1.3; SAS Institute, Cary, NC) to replace missing values for predictor variables.[30] Regression analyses were then carried out on each of the imputed data sets, and the results were combined using functions provided in SAS.[31] The results were very similar to the nonimputed model in which we made missing values a separate categorical level, so we reported the parameter estimates from the imputed model, which used all 829 patients. Predictor variables included age and number of ADGs (both recalculated at the start of each health state using data from the prior 2 years), PSA at diagnosis (grouped as 0–3.99, 4.0–9.99, 10.0–19.99, and $\geq$20 ng/mL), Gleason score at diagnosis (grouped as 2–6, 7, and 8–10), TNM stage[28] (grouped as T1C, T2, T3/4, N+, and M+), and health state. To gain computational accuracy, age and ADG count were centered; that is, the mean, which is a constant, was subtracted from each value with the result that the overall mean of the centered value was zero.

The parameter estimates from the model were used to estimate the median costs of each health state for patients with various characteristics.[32] We exponentiated the parameter estimates from the model so that they could be interpreted as a relative increase in median cost.

We applied a ''smearing estimator''[33] to the median costs estimated by the model to calculate mean costs. The smearing estimate can be computed from the average of the antilogs of the ordinary least squares residuals of the regression model (mean of the exponent of the residuals). In some cases, it may not be appropriate to use the same smearing estimator for all health states or all categories of a parameter. Separate smearing factors for each health state may be a better, alternative approach. Manning[34] suggests interrogating the error structure before applying a smearing estimator. Because this may be particularly critical to the health states in our study, we investigated the residuals from each health state with descriptive statistics, histograms with box plots, and normal probability plots. The variances of the residuals ranged from 0.96 to 1.59, with the exception of the 3 treatment-related health states (RP, RT, and hormone-treated localized PC), which had variances of 0.45 to 0.67. The standard deviations of the residuals ranged from 0.98 to 1.48, except from 0.67 to 0.78 for the 3 treatment-related health states. We interpreted the results of our descriptive analysis as lack of sufficient evidence of the presence of heteroscedasticity in the error across the different health states. We also considered the fact that separate smearing estimates have a disadvantage in that they use only a fraction of the residuals and therefore have a larger variance. For this reason, as well as the lack of evidence of heteroscedasticity, we decided to use a single smearing estimate for all health states.

To assess validity of the model, the data set was divided into a training set (712 patients) to fit the regression model and a test set (117 patients). We compared the predicted costs (estimated using the model developed in the training set) with the actual costs in the test data using the root mean square error (RMSE) criterion for the mean average error (MAE). These are calculated as

$$\mathrm{RMSE} = \sqrt{\frac{1}{n}\cdot\sum_{i=1}^{n}\left(C_i-\hat{C}_i\right)^2}, \quad \mathrm{MAE} = \frac{1}{n}\cdot\sum_{i=1}^{n}\left|C_i-\tilde{C}_i\right|,$$

where $\hat{C}_i$ and $\tilde{C}_i$ denote the estimates for the mean and median predicted costs, respectively, for the ith observation, while C_i denotes the true cost.[32,35] Lower values indicate better predictive ability. RMSE is more suitable as a statistic to compare alternative models. However, for lack of any other measure of validity, we used it to describe our single model and compared the RMSE from our model with those from another

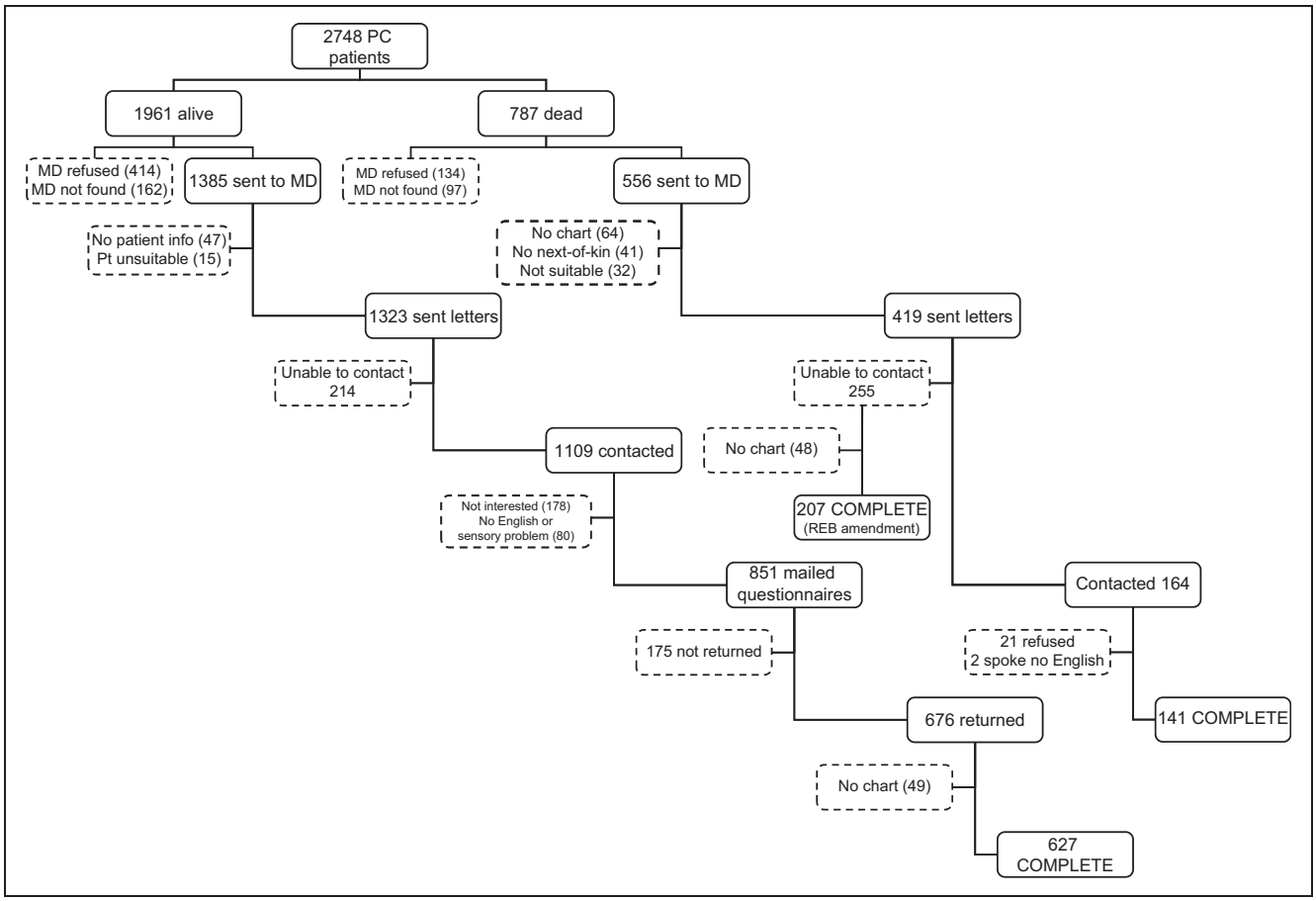

Figure 1 Patient recruitment. PC, prostate cancer.

study[35] relative to the observed mean of the dependent variable (costs) of each study.

RESULTS

Patient Recruitment

Of the 2748 patients selected from the OCR, 1961 were still alive. Figure 1 shows the steps in patient recruitment. We were able to review the charts of 975 patients (627 alive and 348 dead). Three could not be linked to administrative data, so 972 patients were initially included in the study. However, 143 atypical patients (described above) were excluded, leaving a final cohort of 829 patients.

Patients

The clinical and demographic characteristics of the final cohort of patients are shown in Table 1. Their mean age was 66.9 years, and 62% were younger than 70 years. More than 50% had T2 to T4 disease, and 5% had metastatic disease at diagnosis.

Costs and Resource Utilization

The number of patients with observation time in each health state and the mean number of days in each health state are shown in the first 2 rows of Table 2.

Table 2 shows resource utilization per 100 patient-days. The most frequently used resources were diagnostic tests, physician services, and other medical services. Outpatient drug use varied widely, ranging from 2 prescriptions filled per 100 days in the RP group to $\geq$8 per 100 days in patients receiving hormone therapy and those in the late health states (refractory states, metastatic disease, and final). Inpatient days also increased in the later stages of disease.

Table 2 also shows the mean costs in $CAD 2008, unadjusted for patient characteristics, for each

Table 1 Patient Characteristics at Diagnosis (n = 829)

Characteristic	*n*	% or Mean (SD)
Age, y		
<59	156	18.8
60–69	358	43.2
70–79	267	32.2
>80	48	5.8
Age, mean (SD), y	829	66.9 (8.0)
Number of ADGs		
0	4	0.5
1–2	31	3.7
3–5	261	31.5
6–9	383	46.2
>10	150	18.1
ADG count, mean (SD)	829	6.9 (2.9)
PSA, ng/mL		
0–4	82	9.9
4–9.9	327	39.4
10–19.9	194	23.4
>20	154	18.6
Missing	72	8.7
Gleason score		
2–6	337	40.6
7	258	31.1
8–10	148	17.8
Missing	148	17.8
Tumor stage		
T1C	162	19.5
T2	371	44.7
T3/4	82	9.9
Node positive (N +)	8	0.1
Metastatic (M +)	43	5.2
Missing	163	19.7
Income quintile		
1 (low)	114	13.7
2	142	17.1
3	127	15.3
4	182	21.9
5 (high)	254	30.6
Missing	10	1.2
RIO score		
0–9 (urban)	638	77.0
10–44 (suburban)	161	19.4
≥45 (rural)	30	3.6

ADG, ambulatory diagnostic group; PSA, prostate-specific antigen; RIO, Rurality Index for Ontario; SD, standard deviation.

resource and health state. Total costs per 100 patient-days were highest in the early and late health states. Despite the absence of curative therapy during the nontreated nonmetastatic state, costs were relatively high ($3440 per 100 patient-days), with significant amounts for same-day surgery, inpatient stays, and drugs. The most costly initial treatment was RP ($4676 per 100 patient-days), followed by hormone treatment ($3357). Inpatient stays accounted for 65% of costs during the RP health state. Drugs accounted for 41% of costs during hormone treatment. Only 27% of costs during the RT health state were for curative radiation therapy. The 3 middle health states had the lowest costs. Post-RP ($732 per 100 patient-days) was the least costly health state. Costs increased greatly during hormone-refractory metastatic disease ($6398) and 6 months prior to death ($13,739). In the period before death, 65% of total costs were for inpatient hospitalization.

Health States v. Phases of Care

Figure 2 shows the mean costs during the chronologically defined phases reported in our previous study[4] and the costs during the corresponding health states reported in this study. The costs are remarkably similar during the phases (first column in each group) and the health states. However, the phases fail to show the differences in costs between initial treatments in phase II or changes with disease progression during phase IV. Costs during phase V are much higher than in the final health state. The previous study included the atypical older patients with high comorbidity and incidental PC diagnosis who were identified and excluded in the current study. The mean cost in the final health state for the excluded patients was $2000 higher than the cost shown for the included patients.

Predictors of PC Health State Costs

Table 3 shows the relative increases in median cost for each predictor variable, the parameter estimates, and 95% confidence intervals and P values from the multivariable regression with 829 patients.

Age and comorbidity were the most important clinical predictors of costs (both $P < 0.0001$). For every year of age above or below the mean of 67 years, costs increased or decreased, respectively, by 2.5%. Each additional ADG above the mean of 7 increased costs by 8%. High Gleason scores of 8 to 10 were associated with significantly higher costs ($P < 0.001$), as were PSA values above 20 ng/mL ($P = 0.05$). Health state was a significant predictor of costs when all other variables were held constant. Compared with the nontreated nonmetastatic health state, costs were 342% higher in the RP state and 400% higher in the final state ($P < 0.0001$). The 2 metastatic health states had significantly higher costs ($P < 0.05$). Costs

Table 2 Mean Costs ($CAD 2008) and Resource Use per 100 Days per Health State

	Early Health States				Middle Health States			Late Health States			
	Nontreated, Nonmetastatic	RT	RP	HT	Post-RT	Post-RP	Recurrence/ Progression	HT Refractory	Metastatic	Metastatic-Refractory	Final
No. of patients with time in HS	362	274	353	176	243	272	183	46	131	46	284
Mean patient-days in HS	569	464	412	1178	1294	1400	1287	1027	486	427	178
Health care resource											
Diagnostic tests											
Costs	$465	$164	$163	$122	$94	$61	$116	$172	$358	$198	$306
Number of tests	12.33	6.39	7.39	9.43	7.08	5.38	7.45	8.33	11.54	11.59	15.67
Family practitioner visits											
Costs	$72	$63	$66	$78	$64	$50	$61	$78	$93	$85	$137
Number of visits	2.09	1.91	1.90	2.44	2.01	1.52	1.86	2.52	2.69	2.39	3.4
Specialist MD visits											
Costs	$209	$168	$145	$107	$98	$62	$108	$112	$203	$274	$182
Number of visits	4.57	3.69	3.26	2.62	1.96	1.43	2.28	2.87	4.21	4.88	3.59
Nondiagnostic medical procedures, allied health care, miscellaneous											
Costs	$611	$162	$847	$294	$183	$102	$190	$396	$404	$374	$1065
Number of visits	8.19	3.77	7.52	6.60	4.46	3.44	4.70	8.19	9.41	11.55	23.40
Inpatient stays											
Costs	$712	$474	$3031	$1118	$561	$191	$637	$2489	$1334	$3286	$8994
Number of stays	0.19	0.08	0.37	0.17	0.07	0.03	0.08	0.17	0.25	0.37	0.79
Number of days	4.72	1.22	2.04	1.74	1.16	0.49	1.27	7.23	5.00	16.78	11.59
Same-day surgery											
Costs	$749	$84	$190	$96	$85	$63	$127	$47	$239	$69	$160
Number of surgeries	1.18	0.13	0.33	0.15	0.14	0.11	0.18	0.09	0.37	0.12	0.26
Emergency room											
Costs	$30	$18	$27	$35	$16	$14	$27	$48	$40	$64	$193
Number of visits	0.17	0.11	0.16	0.20	0.09	0.08	0.16	0.28	0.23	0.37	1.12
Outpatient drugs											
Costs	$556	$427	$142	$1381	$422	$183	$589	$1070	$1270	$1743	$1197
Number of prescriptions	5.57	4.50	1.86	8.04	5.36	2.23	5.28	8.4	9.49	11.8	18.35
LTC											
Costs	$28	$0	$0	$55	$20	$0	$4	$0	$75	$193	$335
Number of days	0.39	0	0	0.77	0.28	0	0.05	0	1.05	2.72	4.71
Complex continuing care											
Costs	$5	$0	$0	$15	$6	$0	$0	$72	$0	$65	$481
Number of days	0.01	0	0	0.03	0.01	0	0	0.15	0	0.14	101
Homecare											
Costs	$2	$1	$30	$15	$3	$1	$2	$5	$28	$4	$655
Number of visits	0.05	0.02	0.65	0.33	0.07	.020	0.04	0.06	0.11	0.09	12.70
Curative RT											
Costs	$0	$594	$35	$40	$0	$4	$57	$17	$17	$0	$0
Number of fractions	0	5.22	0.29	0.35	0	0.03	0.50	0.12	0.15	0	0
Palliative RT											
Costs	$0	$4	$0	$1	$3	$0	$0	$23	$38	$43	$25
Number of fractions	0	0.04	0	0.01	0.02	0	0	0.01	0.15	0.30	0.25
Total costs	$3440	$2160	$4676	$3357	$1556	$732	$1919	$4503	$4062	$6398	$13,739

HS, health state; HT, hormone therapy; LTC, long-term care; MD, physician; RP, radical prostatectomy; RT, radiation therapy.

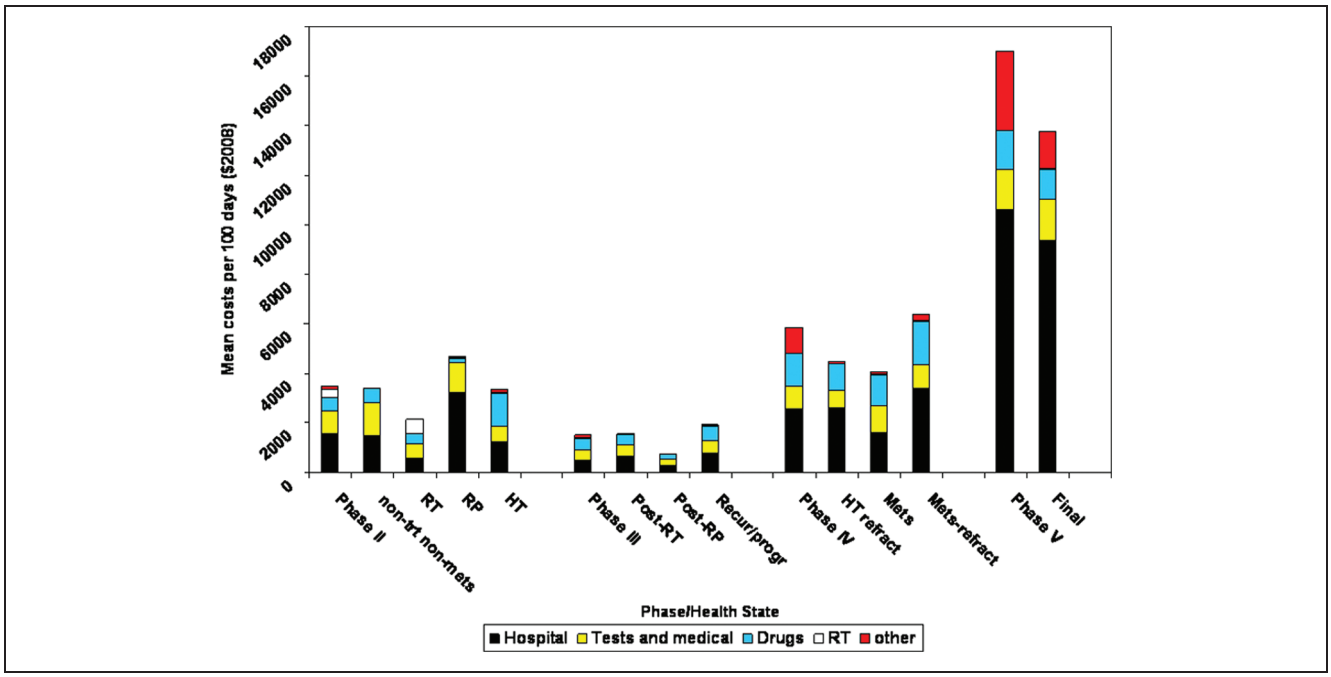

Figure 2 Phase-based cost estimates from our previous study[4] compared with cost estimates for corresponding health states. Phases apply to a cohort of 42,824 patients in our previous study. Phases are defined in reference to 2 index events, cancer diagnosis and death, that can be easily determined using administrative data only. Health states are determined using key clinical events derived from detailed clinical data from chart reviews on a subset (n = 829) of the 42,484 patients. In both studies, patients and the dates of phases or health states were linked to health care administrative data to determine resource use. Costs for resources were estimated using the same established methodologies in both patient groups. Phase I was prediagnosis and not costed in the current study. Radiation therapy (RT) costs were not available for phases IV and V but were included in the corresponding health states. Please see text for further details. The cost categories are as follows: hospital = inpatient stays, same-day surgery, and emergency room visits; tests and medical = diagnostic tests, family practitioners, specialist physicians, and nondiagnostic medical procedures, allied health, miscellaneous; drugs = outpatient prescription drugs; RT = curative and palliative radiation therapy; other = home care, long-term care, and complex continuing care. HT, hormone therapy; RP, radical prostatectomy.

during the post-RT and post-RP health states were significantly lower ($P < 0.0001$), at 29% and 55% of the costs, during the nontreated nonmetastatic health state.

The estimates can be used in the following formula to calculate mean costs: $\exp(\alpha + \beta_1 * X_1 + \ldots + \beta_k * X_k) * S - 1$, where X are the values of each parameter and S is the smearing factor, which is equal to the average of the antilogged residuals from the regression model.[33] Using this formula with our smearing factor of 1.512, the estimated mean cost of the reference case (mean age and ADG count, PSA 4–10 ng/mL, stage T1C, and Gleason score <7 at diagnosis, during the nontreated nonmetastatic health state) is $1981 per 100 patient-days. The estimated cost for the same patient in the RP health state is $6619 per 100 patient-days.

The validity of the statistical properties of the model was assessed by comparing the predicted costs and actual costs from the training and test sets. The RMSE was $5279, and the MAE was $2595. Relative to our mean cost per 100 days over all health states, $4321, the RMSE indicates that the model has good validity. For example, the best models for Cooper and others[35] had an RMSE at least twice the actual mean costs.

DISCUSSION

This study successfully estimated costs to populate a state transition model for PC. By combining detailed chart review with administrative data, we were able to obtain high-quality costs for PC health states, including adjustments for disease-specific and patient-specific variables. This study provides insights into the understanding of PC costs as well as the methodology concerning use of administrative

Table 3 Predictors of Prostate Cancer Health State Costs (n = 829)

Predictor Variable	Relative Cost	Estimate	95% CI	*P* Value
Intercept	1275.865	7.15138		
Age at start of health state (continuous above/below *mean age*)	1.025	0.025152	1.018–1.033	<0.0001
Number of ADGs at start of health state (continuous above/below *mean ADG count*)	1.082	0.079012	1.061–1.103	<0.0001
PSA, ng/mL				
0–4.0	1.076	0.073232	0.902–1.284	0.416
4.1–9.9	1.0			
10.0–19.9	0.918	–0.085506	0.808–1.044	0.191
>20	1.144	0.13443	0.997–1.312	0.055
TNM stage at diagnosis				
T1C	1.0			
T2	1.069	0.066559	0.928–1.230	0.358
T3/4	1.172	0.15862	0.946–1.452	0.160
N +	1.312	0.271227	0.835–2.059	0.255
M +	1.080	0.076971	0.811–1.437	0.598
Gleason score at diagnosis				
2–6	1.0			
7	1.053	0.051683	0.935–1.186	0.394
8–10	1.423	0.352548	1.215–1.666	<0.0001
Health state				
Nontreated nonmetastatic	1.0			
RT	1.166	0.153807	0.973–1.398	0.096
RP	3.432	1.233105	2.866–4.11	<0.0001
Hormone-treated nonmetastatic PC	1.229	0.206047	0.989–1.527	0.063
Post-RT	0.289	–1.240006	0.239–0.350	<0.0001
Post-RP	0.550	–0.598069	0.456–0.662	<0.0001
Recurrence/progression	0.686	–0.376492	0.560–0.840	0.0003
Hormone refractory/progression nonmetastatic	0.799	–0.224773	0.559–1.141	0.216
Metastatic, stable	1.380	0.322412	1.071–1.780	0.013
Metastatic, hormone refractory/progression	1.515	0.415659	1.030–2.229	0.035
Final	3.996	1.385332	3.286–4.860	<0.0001

ADG, ambulatory diagnostic group; CI, confidence interval; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy. The reference case patient is italicized. Mean costs can be estimated as $\exp(\alpha + \beta_1 * X_1 + \ldots + \beta_k * X_k) * S - 1$, where S = smearing factor (1.512). Thus, the estimated cost of a patient aged 67 years (the mean age), with an ADG count of 9 (2 more than mean), PSA <4.0 ng/mL, stage T1C, and Gleason score of 7, during RT = $\exp(7.15138 + (2* 0.079012) + 0.073232 + 0.051683 + 0.153807) * 1.512 - 1$ = $2985/100 days. The estimated cost for the same patient with RP = $8784/100 days. If he were 2 years older, the estimated costs for RT and RP would be $3139/100 days and $9238/100 days, respectively.

data to estimate health care costs for state transition models.

Understanding Changes in PC Costs from Diagnosis to Death

We found that costs for PC patients were highest during the early stages of care and at the end of life, following a ''U''-shaped curve. This pattern has been observed in other PC costing studies that used a phase-based approach.[4,5,36]

We differentiated the ''continuing care'' phase used in other studies[4,36] into 4 health states representing stable follow-up after RP or RT, nonmetastatic recurrence, and hormone-refractory nonmetastatic recurrence. We showed that the lowest continuing care costs were in the post-RP and post-RT states when patients are stable. Costs increased with nonmetastatic recurrence of PC and increased more when patients became refractory to hormone treatment and metastases developed. Figure 2 shows clearly that calculating costs for a single phase between initial treatment and the end of life does not capture these subtle variations in costs as cancer progresses. These distinctions will become more useful as more and higher priced drugs enter the market as therapies for late-stage hormone-refractory PC, thus prolonging survival and introducing additional

health states describing these treatments and their outcomes.

Some PC costing studies followed patients for a specified period after treatment or until death and estimated posttreatment costs.[37–40] Periods ranged from 6 months to 5 years. For RP, mean 6-month costs were reported to be $12,184 ($US 2004),[39] mean first-year costs were $15,197 ($US 2007),[38] and cumulative 5-year costs (both $US 2007–2008) were $19,214[38] and $22,235.[40] These results indicate that the highest costs are within 6 months after RP. Our study found similar annual total health care costs for RP ($17,067). Our RP health state included up to 1 year after treatment but did not include the low-cost post-RP phase or the high-cost period of progression or recurrence. Both would be included in the 5-year cost estimates, but the amounts indicate that costs were lower toward the end of the 5 years, congruent with a low rate of recurrence. However, like the phase-based studies, none of these studies that estimated costs for all patients for the same period considered the actual clinical course of the patients after initial treatment. Health states for recurrence and progression are necessary in state transition models.[13,14] Cost-effective decisions about screening and treatment for PC are highly dependent on these outcomes and their costs.

Methods for Using Administrative Data to Estimate Costs for State Transition Models

We explored a method to improve the quality of costing that took advantage of the strengths of 2 types of patient-level data. The strengths of administrative data are that they are population based, represent large numbers of patients, and are an excellent source of utilization and cost data. The strength of chart review data is their level of clinical detail.

First, we selected patients who had been newly diagnosed over a 10-year period from a province-wide cancer registry. We included deceased patients to sample across the lifetime of PC and sampled from 3 areas of a large Canadian province with different demographics, geography, and access to health care. Second, we retrieved their medical charts to obtain detailed clinical data not readily available in administrative databases, such as PSA levels, physician notes, and Gleason score. We used these data to devise an algorithm to determine the time that each patient spent in health states typical of those used in state transition models. Third, by linking these data back to administrative data, we were able to obtain comprehensive estimates of direct medical costs for each health state.

However, there were some limitations in recruiting the patients, collecting data, and using the data to determine health states. Our method of patient recruitment was costly and labor intensive, and it involved the loss of many patients. A convenience sample including deceased patients from several clinics and physicians' offices would have been easier and possibly as representative, especially if located in different geographical areas. Our study had a high attrition rate, mainly because we could not locate many patients or their referring physicians. As with any voluntary research study, the final sample of consenting survivors may have been biased toward patients who were healthier and more satisfied with treatment. However, we also obtained data from the charts of deceased patients who had no such selection bias.

Collection of data from chart reviews involved planning, consent from many physicians and patients, extensive travel by our team, setting up data entry screens, and manual data entry. Allocating patients' time into health states required substantial programming of the database. We relied on information recorded in the medical chart of 1 physician for each patient. It is possible that important clinical events were missed if a patient failed to follow up with that physician. It might have been possible to allocate patients' observation time into the health states with clever use of administrative data only. Initial treatment information (RP, RT, and HT) is available from administrative databases. In our previous study,[4] we used an algorithm with palliative RT, physician billings for chemotherapy, and diagnostic codes as markers of the development of PC metastases. The dates of these in administrative data, however, would reflect the time of access to treatment rather than the detection of metastases. Recurrence might have been ascertained from HT prescriptions after primary treatment, without resorting to PSA test results and physician notes, but dates would correspond to treatment for, rather than detection of, recurrence. Tumor stage, Gleason score, and PSA at diagnosis were available only through chart review for the years of our study. Tumor stage is being recorded now for many cancer types in the OCR with plans to include these data for all cancer types in the future, and stage and grade of cancer are recorded in the SEER-Medicare data.[3,41] However, the SEER-Medicare data contain month and year, but not day, of diagnosis,[3] which could be essential when examining some outcomes. Administrative data are unlikely to include all variables required for every study.

Most of the data that we used to obtain health care resource use were highly reliable but were collected for the purpose of tracking service. Only the OHIP Claims History Database was used for billing and included actual service costs. We used established costing methods to estimate the direct costs of other services paid for by the Ontario Ministry of Health and Long-Term Care.[4,22,42]

All of the data were available at ICES, except for the RT data, which we obtained from the Radiation Oncology Research Unit database, at Queen's University, Kingston, Ontario. Type of external beam RT was not recorded. We assumed that patients received conventional 4-field RT, the most common type at the time of our study. It is considerably less expensive than conformal RT,[43] which may have been available at some cancer centers in the later years of our study. Therefore, our RT costs may be underestimates.

Costs for each patient were matched by date of service to his health states. The dependent variables in our analyses were the logarithm natural log-transformed total costs per 100 days per health state. The value ''1'' was added to total cost before transformation to ensure that zero costs would be included.

Finally, we collected total health care costs and assumed that most were related to PC and its treatment. Costs were higher in patients with more comorbidity, an indication that all costs were probably not PC related. However, we decided to report total costs rather than PC-specific costs. Even case-control and pre-post studies do not guarantee that disease-specific costs will be accurately estimated. We thought that accurate estimates of real, total health care costs would be more useful for decision models that compare the costs of different PC treatments. Costs do vary with age, comorbidity, and other patient factors. Treatments and course of disease are often dependent on these factors. We chose to represent this real-world situation.

In conclusion, this study has demonstrated an innovative method to calculate high-quality, real-world total health care costs for PC patients that can be used in state transition models for cost-effectiveness or cost-utility analyses. This method can be adapted to other patient populations in which there are administrative health care data with resource use as well as patient identifiers that can be linked to clinical records. Researchers should weigh the potential benefits of using population-based sampling and detailed clinical chart reviews against what is involved in implementing them. Modifications in methodology may achieve similar gains with less outlay in individual studies. Obtaining appropriate costs for health state transition models is challenging and not without its limitations. Overall, however, we believe that this study provides a significant and promising approach toward advancing the quality of costing in state transition modeling.

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