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ORIGINAL ARTICLE

A retrospective analysis illustrating the substantial clinical and economic burden of prostate cancer

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The aim of this study was to determine the treatment patterns and resource utilization of various prostate cancer treatments, and quantify the economic and clinical impact of each. In a retrospective analysis of medical and pharmacy claims between 2000 and 2005, using the PharMetrics database, male patients aged ≥40 years with prostate cancer diagnosis were identified. The costs of medical and prostate cancer-related expenditures for the treatment options were determined for three periods: from diagnosis to first treatment, during and after treatment. A total of 9035 patients were included. The mean age of patients diagnosed with prostate cancer was 61.4 years. Patients aged 50–59 years represented the highest proportion at 51%. The majority received some form of treatment. Watchful waiting (WW) was the primary means of management for 30%. The average 2-year cost for WW was $24 809 and for active treatment was $59 286. Surgery was the most common treatment among younger men. Non-cancer-related costs were similar among those receiving treatment or WW, but prostate cancer costs were over six times greater in the treated patients. With or without treatment, prostate cancer is a significant clinical and economic burden to society. New strategies for treatment or cancer prevention could play a role in reducing this burden.
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Introduction

Prostate cancer is the most prevalent cancer in males, affecting one man in every six.[1] The American Cancer Society had estimated that 186 320 were diagnosed with prostate cancer and approximately 28 660 died from the disease in 2008.[2] These estimates make prostate cancer the most frequently diagnosed cancer of all new cases (25%) and the second most common killer cancer (10%).[2] Furthermore, prostate cancer is a leading cancer in terms of costs. Estimates in US dollars as made in 2004 using the Medicare SEER data reported by the National Cancer Institute (NCI) found $8 billion in total medical expenditures attributable to prostate cancer (11.2% of all cancer treatment expenditures), just after lung ($9.6 billion, 13.3%), breast ($8.1 billion, 11.2%) and colorectal ($8.4 billion, 11.7%).[3] These costs are expected to rise with the aging population and as more advanced treatment modalities and technologies emerge.[3]

Once a male is diagnosed with prostate cancer, management decisions are complex. Treatment depends on factors such as cancer stage, patient's age, existing co-morbidities and other patient-specific risk factors. The most common management approaches are watchful waiting (WW) (also known as expectant management, deferred therapy or surveillance), surgery (for example, radical prostatectomy) and radiation therapy (for example, external beam radiation and internal beam radiation/brachytherapy). The core argument for WW is that prostate cancer patients tend to die 'with' and not 'of' the disease,[4,5] often leading to debate in the medical community regarding the need to treat prostate cancer. This debate and variation in treatment patterns has lead to a lack of clarity as to what the real-world treatment patterns are, the attributable costs of care with each approach, and at which point in the process of care do patients incur the highest medical resource consumption. While other investigations have presented costs associated with prostate cancer,[6,7] differences based on treatment approach are not well established. This study seeks to provide a greater understanding of the true clinical and economic outcomes and implications of the different approaches to treating prostate cancer in a managed care population.

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Materials and methods

Data source

Pharmacy and medical claims were identified between July 2000 and May 2005 in the PharMetrics database,

which contains over 85 health plans and covers over 45 million lives. Data obtained from PharMetrics were prescription records, diagnostic data per the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes[8] and procedures per the Current Procedural Terminology-4 (CPT-4) codes.[9] Dates including paid and charged amounts were available for all services provided.

Sample selection

Male patients aged ≥ 40 years and diagnosed with prostate cancer between July 2000 and May 2005 were identified. Patients were included if they had an ICD-9-CM code for prostate cancer (185, 233.4) and were continuously eligible for at least 30 months (6 months prior to diagnosis and a minimum of 24 months post diagnosis). Patients were excluded if they had any ICD-9 claims for any other cancer types.

Outcomes analysis

Treatment characterization and utilization. Patients were placed into either the WW cohort or one of six treatment cohorts based on the initial type of treatment received. Patients under WW were defined as those who received no treatment for prostate cancer during the entire assessment period. These patients were required to have two separate prostate cancer diagnoses to be included in the study. For those receiving treatment, treatment options included surgery (that is, prostatectomy), hormone (for example, luteinizing hormone-releasing analogs (LHRH), LHRH antagonists and anti-androgens), chemotherapy, radiation and alternative treatments (for example, ketoconazole, aminoglutethimide and corticosteroid). Patients who received two treatments at index were classified as multiple; however, all cohorts could have had additional treatments after their index treatment. For the purposes of this study, patients who had WW and subsequently went on to treatment were classified under the respective treatment option.

Time to treatment, defined as the number of days between diagnosis and the first day of first treatment, was evaluated for the various treatment options. The mean duration of therapy and the time between the day of initiation of first treatment to the last treatment, was also determined.

Treatment cost analysis. Resource costs were categorized into two main groups: disease-specific and non-disease-specific. Disease-specific costs were direct medical costs of care related to treatment procedural costs, physician costs, inpatient hospitalizations, outpatient visits, hospital care and emergency department visits. Within the disease-specific analysis, prostate-related costs were also computed and were composed of costs on claims with a primary ICD-9-CM code of 185 or 233.4. Non-disease-specific costs were those that did not fall under the definition of disease-specific. The average total monthly medical costs per patient were calculated from 6 months prior to prostate cancer diagnosis (for baseline comparison) through 24 months after diagnosis.

Beyond costs, screening and diagnostic measurements and trends 6 months prior to the cancer index date were assessed. In addition, the incidence of clinical adverse events for each treatment option was examined. The costs related to the occurrence and treatment of adverse events was not included in the analyses.

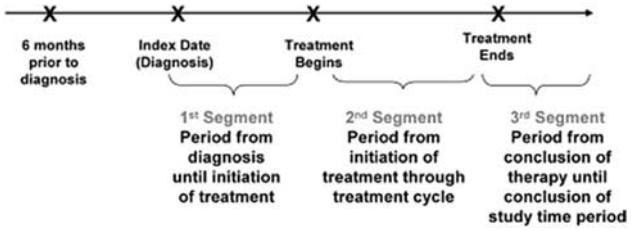

Figure 1 Process of care—outcome measurement segments.

Process of care measurement segments. Treatment costs were determined in three period segments, as delineated in Figure 1, to measure the before treatment (post-diagnosis), during treatment and after treatment-related costs for the various treatment options.

In the first segment analysis, the index date is defined as the date of the initial diagnosis for prostate cancer. Costs calculated from the first segment cover the index date through just prior to the first documented treatment initiation. The second segment covers the time from treatment initiation through the entire length of the treatment period. In the third segment, costs are calculated from the last treatment on record through the end of the study time period (defined as 24 months after diagnosis). Due to varying treatment duration and follow-up times of the different treatment options, the mean annual and monthly charges were calculated for each patient over the length of that individual's therapy.

Statistical analysis. Descriptive summary statistics were constructed as frequencies and proportions for categorical data and means for continuous variables. No statistical analyses were performed.

Results

Patient distribution and treatment characteristics

A total of 9035 patients with prostate cancer diagnosis were identified and included in this analysis (Figure 2). Patients in this study had a mean age of 61.4 years, with 51% of men being between 50 to 59 years of age.

The majority of men (70%) received some form of active treatment during follow-up, while 30% of men appeared to undergo WW as their primary means of prostate cancer management (Table 1). Of the actively treated patients, surgery was most often initiated among men of younger age (mean age = 57.7 years). The use of hormonal treatment was associated with older men (mean age = 65.1 years), while the age distribution for WW, radiation, chemotherapy, multiple treatments, and miscellaneous treatments were similar.

Among active treatment, surgery was performed earliest, at an average of 71 days (2.3 months) after

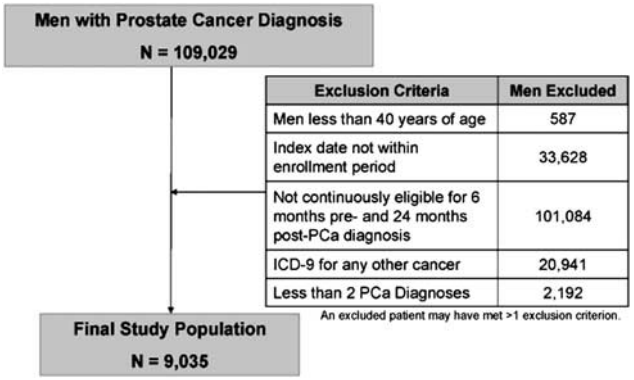

Figure 2 Patient selection.

Table 1 Distribution, mean age, and mean time to treatment of patients by assigned treatment group

	% of Patients (initial)	*Mean age (years)*	*Time to treatment (days)*
Watchful waiting	30.4	62.8	—
Surgery	28.8	57.7	71
Radiation	11.0	62.5	91
Hormonal therapy	17.1	65.1	93
Chemotherapy	0.3	60.1	80
Miscellaneous[a]	11.6	60.5	277
Multiple	0.8	61.4	—

[a]Miscellaneous refers to alternative or ancillary treatments such as ketoconazole, aminoglutethimide or corticosteroid use.

diagnosis, occurring at least 30% sooner than any other forms of treatment. The majority (77%) of patients received only one type of treatment, while approximately 23% received two or more. Patients who received chemotherapy initially were most likely to have additional treatments after chemotherapy (63%), followed by patients receiving hormone therapy (61%).

When evaluating treatment trends over time, the rates of prostate cancer surgery were observed to have increased consistently from 18% in 2000 to 38% in 2004, while rates of hormone therapy have declined from 25% in 2000 to 15% in 2003 (Figure 3). Patients undergoing WW have decreased from 37% in 2000 to 23% in 2004.

Prostate cancer costs of care

The average total expenditures for the 2-year period after initial prostate cancer diagnosis were $48 807, with 52.3% ($25 514) representing prostate cancer-related costs. The average disease-specific 2-year cost for WW was $5446 and for active treatment was $34 277. Prostate cancer costs were over 6 times higher in treated patients, being largely driven by the costs of the varying prostate cancer treatments. The majority of these costs were incurred within the first year. Non-disease-specific costs were comparable between patients receiving treatment and WW. The average 2-year non-disease-specific costs were $25 009 for patients receiving treatment and $19 363 for WW patients.

Evaluation of prostate cancer costs of care over time revealed that the highest costs were incurred within the

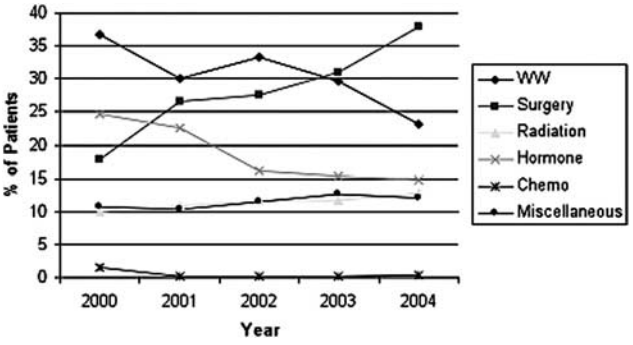

Figure 3 Prostate cancer treatment trends.

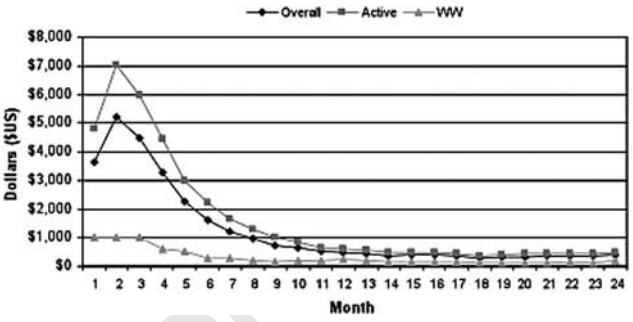

Figure 4 Average prostate cancer-specific monthly medical costs.

first 3 months of diagnosis and decreased substantially over time (Figure 4). By 9 months after diagnosis, medical costs for actively treated patients averaged less than $1000 per month, and decreased to less than $500 per month at 24 months. WW patients averaged approximately $1000 in medical care during the first 3 months, with costs reducing to approximately $200 per month thereafter.

Evaluating cancer-related costs across segments of care indicated that 11.7% of the cost of care was incurred during pretreatment, 81.9% resulted during the treatment period itself and the remaining 6.4% made up the costs for follow-up care after treatment.

Excluding patients with combination therapy, patients who initially had surgery incurred costs of $32 470 over their treatment duration (Figure 5). The majority of these costs were due to inpatient resource utilization ($26 834). The most highest treatment cost was for those patients who initially had radiation, costing $50 926 over their treatment duration, with over half of the costs due to outpatient resource utilization ($22 751). Patients receiving combination therapy including radiation were the ones with the costliest of all combination therapies: they incurred costs of $52 505, with $26 729 due to outpatient resource utilization.

An evaluation of yearly trends with prostate cancer-related costs indicated that costs increased over all treatment types with the exception of miscellaneous. The cost of treating prostate cancer rose most substantially for radiation and surgery followed by hormone therapy (Figure 6).

An assessment of clinical events indicated that, in general, men who received treatment were more likely to have an adverse event coding (incidence ranged from

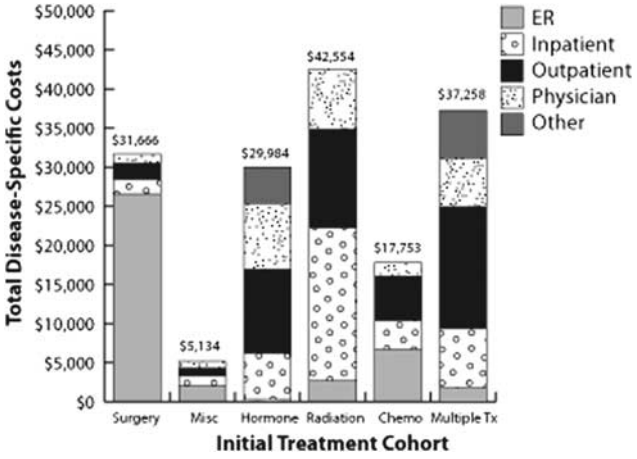

Figure 5 During-treatment medical resource utilization.

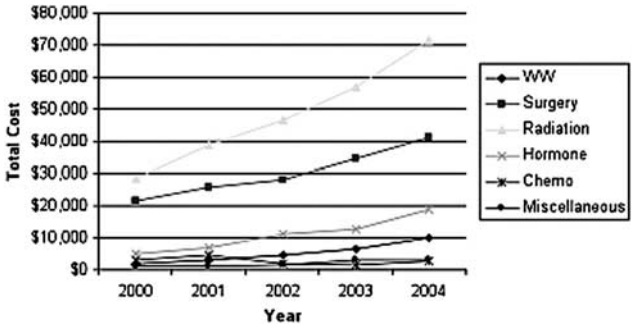

Figure 6 Prostate cancer cost trends.

Table 2 Patient-reported clinical events on treatment and with WW

Clinical events	*Surgery (%)*	*Radiation (%)*	*Hormonal (%)*	*Chemo. (%)*	*Misc. (%)*	*WW (%)*
Overall	86	67	66	51	37	49
Impotence	29	12	12	12	8.8	13
Urinary incontinence	24	10	14	10	6.4	8.4
Anemia	13	6.2	11	12	4.4	5.4
Urinary retention	12	11	10	7.1	3.7	3.9
Urethral stricture	10	5.2	6.5	8.1	1.9	2.5
Hematuria	8.2	9.5	9.9	7.1	4.0	5.8
Fatigue	4.2	5.3	4.5	9.1	2.5	3.9
UTI	4.1	3.3	3.5	3.0	0.9	2.4
Dysuria	2.1	5.1	3.4	3.0	1.6	1.0
Nausea	0.9	0.6	0.8	5.1	0.5	0.7
AEs not listed	72	51	50	40	27	29

Abbreviations: AE, adverse event; Misc, miscellaneous; UTI, urinary tract infection; WW, watchful waiting.

37 to 86%) than men under WW (49%). Surgical patients had the highest rate of adverse events. Some of the common adverse events are listed in Table 2.

Discussion

The purpose of this study was to provide a greater understanding of the patterns of prostate cancer care, while highlighting the clinical and economic implications for various treatment approaches. Although controversy exists regarding appropriate treatment and management of prostate cancer, the majority of men received some form of active treatment. Surgery was the most common and rapidly growing option, while being associated with men of younger age (that is, <60 years of age). This observation is consistent with the published literature and clinical practice guidelines, which promote prostate surgery in men with a life expectancy of at least 10 years.[10–12] Prostatectomy has been shown to reduce disease-specific and overall mortality, including risk for disease progression and metastasis, particularly in men less than 65 years of age.[11]

The monthly and yearly cost differences found in this study were similar to those in other investigations,[6,7] although direct comparisons are difficult due to differences in study populations and designs. Additionally, these other studies do not report differences in costs related to different treatment patterns. For example, a retrospective case–control analysis of a commercially managed care database found monthly costs for patients with prostate cancer to be $2187, while controls without cancer had monthly costs of $343.[6] The costs for prostate cancer over 1 year add up to $26 244 in comparison with the annual costs of $25 514 in this study. Comparisons can be made with a retrospective cohort evaluation of patients treated within a single health system from 1995 to 2000, investigating the economic burden in men with prostate cancer both before and after disease progression.[7] This analysis examined costs both before and after metastatic progression, as well as costs both before and after PSA progression. In those classified with metastatic progression, mean (±s.d.) costs were $24 538 ± $20 907 and $34 093 ± $30 558 before and after progression, respectively, after 1 year. In those classified with PSA progression only, mean (±s.d.) costs were $9022 ± $10 539 and $12 455 ± $17 325 before and after progression. The Penson *et al*. analysis controlled for treatment, and thus, did not report differences in costs at the treatment level as in this study.

In addition to being the fastest growing treatment, the cost of surgical treatment was substantial and rose steadily each year. Monthly treatment costs averaged about $6870 per patient for 4.7 months, yielding costs of care for surgery alone of over $32 000 per patient. Surgery had the highest coded clinical adverse events (at 86%) of any treatment type. Urinary incontinence and impotence were reported in over 20% of patients. These rates were likely lower than actual rates since they only included adverse events that were coded. The actual rates of urinary incontinence and impotence from prospective studies have been shown to be higher.[13] In a prospective study to evaluate the functional results after retropubic and laparoscopic radical prostatectomy, rates of incontinence were found to be approximately 34 and 13%, respectively, for the two surgical procedures at 1 year. Rates of erectile dysfunction were 31 and 41%, respectively. In another prospective investigation in a community practice, incontinence rates reached 90% and potency rates reached 79% with bilateral nerve sparing technique and 54–86% in academic series at 5 years.[14] These adverse events are likely to be underreported in claims databases such as the one analyzed for this investigation.

Given the adverse events associated with cancer treatments, and the costs of care, it was not surprising that some men are still opting to undergo a more conservative approach of WW. However, the percentage of men undergoing WW decreased from 37 to 23% in the study timeframe. The percentages in our study are substantially higher when compared with published estimates, which currently estimate WW at approximately 10%.[15] This is likely due to the fact that WW patients had a diagnosis of prostate cancer, but did not receive treatment during the study period. The absence of treatment after diagnosis may be reflective of ruling out prostate cancer instead of true WW. Even with the potential of misclassification as seen in this study, WW has been accepted as an alternative for patients who are unlikely to benefit from or tolerate more active treatment interventions.[16] Clinical practice guidelines recommend WW when the patient has a life expectancy of less than 10 years or if the cancer risk is low. However, WW in itself is not without expense, risk and quality-of-life issues. The 2-year cost of care related to WW was $24 809 per patient, mainly due to multiple follow-ups and close monitoring that takes place in the observational approach to care. Despite a much lower proportion of reported clinical events compared with treatment, 49% of men under watchful observation had a coded adverse event. The most commonly coded events were impotence, hematuria, urinary incontinence, anemia and fatigue. In addition, the psychological effect of the uncertainties and anxieties related to the knowledge of presence of the disease (but without active treatment) has been reported to negatively impact the patient's quality of life.[17,18] While WW remains a viable clinical alternative, its costs and impact on quality of life are considerable.

This study indicates that with or without active treatment, prostate cancer places an enormous clinical and economic burden on patients and the healthcare system. Development of new and effective treatment strategies could significantly reduce this burden and fundamentally change the approach to prostate cancer management. Additionally, the study may also suggest that more preventive approaches may be warranted. Although the Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed that various over-the-counter medications are not effective in preventing prostate cancer at conventional doses,[19] treatment with 5-α-reductase inhibitor (5ARI) therapy may be promising. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial indicated that dutasteride significantly reduced the risk of all biopsy-detectable prostate cancer by 23% over 4 years, compared against those who took placebo, in more than 8100 men aged 50 to 75 years.[20,21]

This study has several limitations. First, the retrospective nature limits the amount of clinical information available (such as cancer grade), which would be valuable in understanding the treatment patterns. Due to lack of clinical information, it is unclear whether the treatment practices in this study reflect emerging clinical practice trends. Additionally, patients were required to be eligible for at least 2 years after diagnosis. The relatively short time constraints may have several consequences, including (1) not enough follow-up to follow men until death; (2) database did not contain death records and (3) database did not contain records of hospice or end-of-life care. As such, patients who may have died of prostate cancer were not considered in this study and the costs of prostate cancer are likely undervalued. In addition, this analysis did not include the costs of adverse events that may have been a result of therapy. Therefore, the costs presented in this study may be lower than the true costs of prostate cancer care. Given the nature of this retrospective analysis, it was not possible to distinguish between a patient who purposefully went on WW and a patient who had a delay in therapy. The study methods categorized the latter into treatment groups once the respective treatment had begun. As such, the time to starting treatment therapy may actually be a result of a period of intended WW preceding deliberate timing of treatment.

Moreover, since data were collected from a specific managed care database, generalizations of these results are cautioned. Specifically, the use of a managed care database limits the generalizability of the results to a much older Medicare population. Indeed, data from the SEER-Medicare project illustrate that the relatively older Medicare population has higher costs than the overall population with prostate cancer.[22] Prostate cancer moves from the most expensive single cancer to the fourth most expensive single cancer.[22] Thus, the findings from this study of a relatively younger, managed care population cannot be broadly applied to older populations.

Conclusions

With or without treatment, prostate cancer is a significant clinical and economic burden to society. With the continuing growth of the aging population, new strategies for treatment or prevention could play a substantial role in reducing the patient burden and healthcare costs. In 2003, the Prostate Cancer Prevention Trial (PCPT) found that treatment with a 5ARI, finasteride, resulted in 24.8% risk reduction of prostate cancer over those treated with placebo over a 7-year period.[23] The recently completed REDUCE trial indicated that dutasteride, a more comprehensive 5ARI than finasteride (that is, both isoenzymes), reduced prostate cancer risk by 23% within 4 years.[20,21,24] If such therapies are found to be both safe and effective, they may also represent an opportunity to reduce the impact of costly prostate cancer treatment interventions, not only in economic terms but also in humanistic terms encompassing patient quality of life.

Conflict of interest

Drs Eaddy and Kruep are employed at Xcenda. Dr Crawford received an honorarium from Xcenda for his professional services relevant to this study and the paper. Dr Black is employed at GlaxoSmithKline.

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