Using a Transition Model with Survival Weights to Analyze Cost-Effectiveness and Cost Utility: A Case Study Applied to Finasteride for the Prevention of Prostate Cancer

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1 Abstract

Background

Cost-effectiveness and cost-utility often rely on Markov modeling, which is dependent on model assumptions and is subject to incorrect specification of model inputs. Our objective was to develop a transition model with observed survival weights to analyze cost-effectiveness and cost-utility, and to apply this method to finasteride, a 5alpha-reductase inhibitor which can limit the development of prostate cancer.

Methods

Using the new approach, we performed cost-effectiveness (life-years) and cost-utility analysis (quality-adjusted life years) of finasteride in a hypothesized population of 1,000 men, age >=55 years, with a 10-year time horizon. Survival weights were derived from Surveillance, Epidemiology, and End Results (SEER) data and estimates of normal survival from the life tables of the National Center for Health Statistics. Finasteride efficacy parameters were based on recent studies showing a model-specified reduction in prostate cancer of 34% for low grade cancers and 27% for high grade cancers. Utility scores were derived from the SF-6D.

Results

The cost-effectiveness ratio for finasteride was $68,379 per life year (base case). In men ≥65 years, the cost-effectiveness ratio was $52,663 per life year. Cost-utility estimates were higher due to modest negative side effects of finasteride on sexual function, with $77,592/quality-adjusted life year (QALY) using linear mixed models and $88,845/QALY using pattern-mixture models.

Conclusions

The proposed transition model has the advantage of using observed population survival weights to implicitly represent the transitions between states that can occur for those developing cancer. A case study applying this method showed that finasteride may represent a cost-effective approach (i.e., <$100,000 per quality-adjusted life year) to reducing the incidence and subsequent mortality from prostate cancer in the general population of older men.

2 Background

Markov Models, Strengths and Limitations

- Markov models allow simple and intuitive approach to model both costs and outcomes[1]
  - Useful for cost-effectiveness
- However, they rely on "Markovian" assumption of memoryless transition between states[2]
  - Transition from state to state independent of prior transitions
- Attempts to modify:
  - Model processes separately according to different patient histories
  - Use time-dependent Markov processes

ALTERNATIVE

- Develop a transition model and rely on actual **observed population data** that implicitly incorporate transitions between states (i.e., "survival weights")

1 – Sonnenberg and Beck, Med Dec Making, 1993
2 – Briggs and Sculpher, Pharmacoeconomics, 1998

Finasteride for the Prevention of Prostate Cancer

- Prostate cancer 2nd most commonly diagnosed cancer in men (192,000 cases and 27,000 deaths in 2009)[3]
- SWOG conducted PCPT in mid-1990s to test whether finasteride limits development of prostate cancer[4]
  - Finasteride is a potent antiandrogen that inhibits 5-alpha-reductase, an enzyme crucial to develop prostate cancer
  - Double-blind placebo controlled trial, N=18,000
- Results showed 25% REDUCTION in period prevalence, BUT also an observed INCREASE in rate of high grade tumors (Gleason 7-10)
- Finasteride found not to be cost-effective[5]

Meanwhile…

- Recent research found that observed increase in high grade tumors due to biopsy sensitivity[6]
- Detailed review of grading results found 27% relative risk REDUCTION of high grade cancer
  - Also 34% reduction in low grade cancers (updated)
- Therefore uncertainty about net clinical benefit and value (cost-effectiveness) of finasteride

3 – National Cancer Institute, http://www.cancer.gove/cancertopics/types/prostate
4 – Thompson et al., NEJM, 2003
5 – Zeliadt et al., Amer J Med, 2006
6 – Redman et al., Cancer Prev Res, 2008

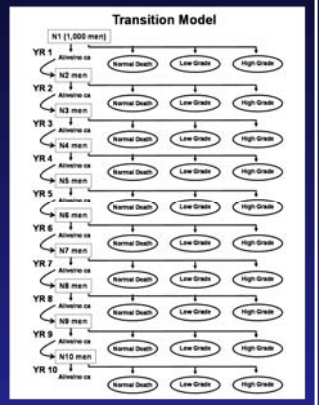
3 Objectives

- To develop a transition model with observed survival weights to analyze cost-effectiveness and cost-utility
- To apply this model to finasteride for the prevention of prostate cancer

4 Methods

The Model

- Transition model with survival analysis to calculate life-expectancy weights
- Hypothesized cohort of N=1,000 men over 10 years (see Figure)
- Individuals alive without cancer can transition to alive without cancer, normal (non-cancer) death, low grade prostate cancer, or high grade prostate cancer
- Latter 3 states "absorbed" and contribution to life years estimated thru survival function (by calculating the area under the survival curve)
- Using survival function replaces Markov modeling, with observed survival capturing varied set of possible outcomes for person developing cancer (i.e. transition to higher grade, treatment with possible later recurrence, or death)



The Prostate Cancer Prevention Trial

- 18,882 men ≥55 years randomized to finasteride daily or placebo for 7 years
- Normal digital rectal exam and PSA≤3.0 ng per milliliter
- Study closed early with 25% overall reduction of prostate cancer but 67% increased risk of high grade tumors

Model Parameters from PCPT

- 34% reduction in low grade and 27% reduction in high grade cancers (excluded "unknown" grade from base case) (Redman et al., 2008)

Cancer Population Model Parameters

- Use 1997-2006 SEER data[7]
  - Include incident cases of local/regional, distant, and unstaged disease, for men >=55 years
- Age and stage weighted according to age and stage distributions of men with any grade prostate cancer in SEER during the period

Table: SEER Age-Specific and Weighted Overall Prostate Cancer Incidence Rates

	Prostate Cancer Incidence/1000			
Age At Diagnosis	Low Grade (Gleason 2-7)	Grade III (Gleason 2-8)/-Undifferentiated	Unknown Grade	Overall Prostate Cancer Rate/1000
55-59	2.30	0.91	0.09	3.3
60-64	3.96	1.68	0.18	5.81
65-69	5.96	2.62	0.33	8.91
70-74	6.74	3.01	0.49	10.25
75-79	6.23	3.26	0.70	10.19
80-84	4.37	3.12	1.07	8.56
85+	2.45	2.61	2.17	7.24
Weighted Average*	4.52	2.18	0.46	7.16

* Age-weighted according to SEER any grade prostate cancer population

Estimates of Non-Cancer Death

- From life tables of the National Center for Health Statistics[8]
- 2001 data (midpoint of the 1997-2006 interval)
- Weighted according to the age and stage distributions of any grade prostate cancer patients from SEER for consistency

Costs

- Finasteride costs estimated at $2.03/pill using 2009 1-year supply[9]
- Stage-weighted estimates, inflated to 2009 dollars, were $13,590 for initial care and $593/year for continuing care costs[10,11]

Utility Estimation

- Used SF6D, a preference weighted outcome measure derived from SF36 (baseline, 6 months, and annually through year 7)[12]
- To model SF6D outcomes, used both linear mixed models (assumes missing at random) and pattern-mixture models (allows modeling under NMAR)[13,14]
  - For pattern-mixture models, included dropout pattern as covariate (binary: dropout > 2 years vs. <=2 years)

7 – SEER website, www.cancer.gov, 1973-2006
8 – Arias E. United States Life Tables, NCHS, 2004
9 – Drugstore.com, December 15, 2009
10 – Taplin et al., JNCI, 1995
11 – Consumer Price Index, Detailed Report, online at http://www.bls.gov/schedules/archives/cpi_nr.htm
12 – Brazier et al., J Clin Epidemiol, 1998
13 – Brestow and Clayton, JASA, 1993
14 – Little and Wang, Biometrics, 1996

5 Results

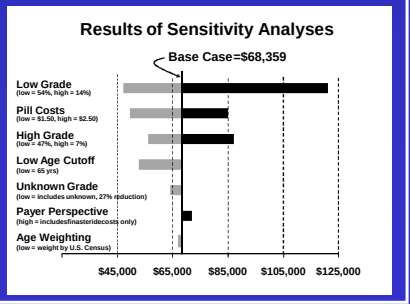
Cost-Effectiveness

Life-years (out of 10,000 possible):
Men on finasteride = 8,275.2
Men without finasteride = 8,190.0
Net gain = 85.2 life-years (0.0852 per man receiving finasteride)

Costs
Finasteride costs ($2.03/pill):
For men on finasteride = $6,126,882
For men without finasteride = $0

Total initial treatment and continuing care costs:
For men on finasteride = $667,234
For men without finasteride = $968,808
Net difference = $5,825,308 attributable to finasteride

Cost-Effectiveness Ratio
$68,370 per life year gained



6 Results (cont'd)

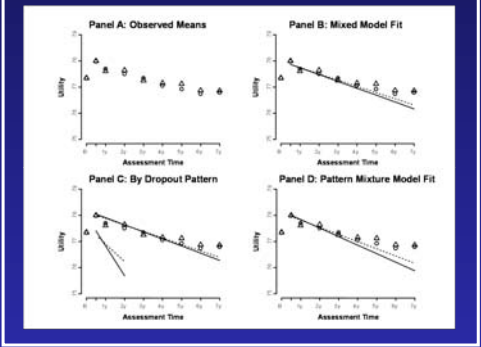
Cost-Utility

- Observed mean utility scores decrease over time (Panel A)
- Greater decrease for finasteride participants (Panel B)
- Greater dropout over time for finasteride participants (Table)
- Differential utility patterns by dropout time (Panel C)
- Greater modeled difference between placebo and finasteride utility scores accounting for dropout patterns (Panel D)

Cost-Utility Ratio
Mixed Models = $77,592 / QALY
Pattern Mixture Models = $88,845 / QALY

Dropout Patterns

	Percent Missing	
Assessment Time	Finasteride	Placebo
6 Months	10%	8%
1 Year	13%	9%
2 Year	23%	17%
3 Year	29%	23%
4 Year	34%	27%
5 Year	38%	32%
6 Year	42%	36%
7 Year	48%	43%



7 Limitations

- In this study, preferences modeled on a healthy cohort
  - PCPT required normal digital rectal exam at baseline (i.e., no BPH)
- Thus using SF6D on PCPT cohort misses the positive impact of finasteride on prevalent cases of BPH
  - Results of this analysis represent a conservative upper bound on CU ratio
- Could rectify with additional modeling assumptions (e.g., "community rating")
- No analyses of other targeted high risk populations (African Americans, men with family history)

8 Conclusions

- The proposed transition model has the advantage of using observed population survival weights to implicitly represent the innumerable transitioning between states that can occur for those developing cancer
- Finasteride is a proven effective chemopreventive agent for prostate cancer with low side effects and demonstrated cost-effectiveness (<$100,000/QALY)
- Finasteride could have large potential impact on incidence and subsequent mortality from prostate cancer in general population of older men

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