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Effects of Family History and Genetic Polymorphism on the Cost-Effectiveness of Chemoprevention With Finasteride for Prostate Cancer

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Abstract

Purpose—Improvement in the cost-effectiveness of chemoprevention for prostate cancer could be realized through the identification of patients at higher risk. We estimated the cost-effectiveness of prostate cancer chemoprevention across risk groups defined by family history and number of risk alleles and the cost-effectiveness of targeting chemoprevention to higher-risk groups.

Materials and Methods—We developed a probabilistic Markov model to estimate costs, survival, and quality-adjusted survival across risk groups for patients receiving or not receiving chemoprevention with finasteride. The model uses data from national cancer registries, online sources, and the medical literature.

Results—The incremental cost-effectiveness of 25 years of chemoprevention with finasteride in patients aged 50 years was an estimated \$89,300 per quality-adjusted life-year (95% confidence interval, \$58,800–\$149,800), assuming finasteride reduced all grades of prostate cancer by 24.8%. Among patients with positive family history (without genetic testing), chemoprevention provided 1 additional QALY at a cost of \$64,200. Among patients with negative family history, at \$400 per person tested, the cost-effectiveness of genetically targeted chemoprevention ranged from \$98,100 per QALY when limiting finasteride to patients with 14 or more risk alleles to \$103,200 per QALY when including patients with 8 or more risk alleles.

Conclusions—Although there are small differences in the cost-effectiveness of genetically targeted chemoprevention strategies in patients with negative family history, genetic testing could reduce total expenditures if used to target chemoprevention for higher-risk groups.

Keywords

Chemoprevention; Cost-Benefit Analysis; Finasteride; Polymorphism; Genetic; Risk Factors

Introduction

Cost-effectiveness analyses of chemoprevention with finasteride for prostate cancer have shown that each additional year of survival would cost \$1.1 million to \$1.7 million.^{1,2} After adjustment for differences in quality of life, the incremental cost-effectiveness ratios

(ICERs) ranged from \$123,000 to \$200,000 per quality-adjusted life-year (QALY).^{2,3} Improvement in the cost-effectiveness of chemoprevention could be realized through identification of higher risk patients.³ Recent studies have identified genetic variants associated with increased risk of prostate cancer.^{4–9}

Using data from the Cancer of the Prostate in Sweden (CAPS) study and the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO) in the United States, Xu et al¹⁰ published a prediction model that uses 14 5-single-nucleotide polymorphisms and family history to estimate an individual's risk of prostate cancer. To evaluate the impact of targeted chemoprevention on the cost-effectiveness of finasteride, we used this risk-prediction model to develop a computer simulation model in Microsoft Excel to estimate costs, survival, and quality-adjusted survival for risk groups defined by family history and number of risk alleles. We also evaluated the cost-effectiveness of genetic screening and targeted chemoprevention strategies, accounting for the prevalence of inherited risk alleles and family history of prostate cancer in the population.

Methods

The Markov model in this study represents 8 distinct health states (Figure 1). We assumed all patients were free of prostate cancer at time zero. In annual cycles, patients could develop low-grade (Gleason score 2 to 6), intermediate-grade (Gleason score 7), or high-grade (Gleason score 8 to 10) prostate cancer. Patients then underwent treatment and remained in that health state until death from other causes or biochemical recurrence of prostate cancer. Patients with biochemical recurrence could survive with recurrence, die of other causes, or progress to metastatic disease. Patients who progressed to metastatic disease could survive with cancer, die of cancer, or die of other causes.

We generated age-specific rates of prostate cancer incidence for patients not receiving chemoprevention (DevCan version 6.4.1; National Cancer Institute) and data from the Surveillance, Epidemiology and End Results database for 2000 through 2006.¹¹ Distributions of cancer grades were based on for-cause biopsies in the placebo group of the Prostate Cancer Prevention Trial (PCPT).¹² All-cause age-specific mortality rates were based on 2001 US life tables.¹³

Base-Case Assumptions

We designed the cost-effectiveness model to represent the health care system perspective. Table 1 summarizes the base-case estimates, including point estimates, standard errors, and distributions applied in probabilistic sensitivity analyses. We applied a 3% annual discount rate to costs and survival. Patients entered the model at age 50 years.

Patients in the chemoprevention strategy initiated daily use of finasteride for 25 years or until they developed prostate cancer. We applied a constant 24.8% risk reduction with finasteride to all tumor grades and assumed the effect was maintained through 25 years.¹² We applied a 14.7% nonadherence rate based on the percentage of treatment days missed during follow-up in the PCPT.¹² Although this rate lowered the cost of chemoprevention, we did not adjust the effectiveness measure, because the treatment effect in the PCPT reflected this nonadherence rate. Transition probabilities for biochemical recurrence, development of metastatic cancer after biochemical recurrence, and mortality attributable to prostate cancer were based on outcomes of patients after radical prostatectomy.^{14,15} Consistent with previous economic evaluations,³ we set the prevalence of BPH at 15% in patients younger than 75 years and 22% in patients aged 75 years or older. We assumed finasteride reduced the prevalence of BPH by 40%.¹⁶

Costs

Medical costs associated with prostate cancer in the year after diagnosis, the year before death, and all intervening years were derived from a recent study (Table 1).^{17,18} In assigning costs for outpatient medications, we assumed patients with BPH were treated with alpha-blockers and patients with biochemical recurrence or metastatic disease received androgen suppression therapy. Costs of chemoprevention consisted of the cost of finasteride.

Subgroups

We estimated the impact of family history of prostate cancer and the number of inherited risk alleles from Xu et al.¹⁰ in which the odds ratios represented the odds of prostate cancer in patients with a given family history and number of risk alleles compared with patients with negative family history and 11 risk alleles. In the model, we converted odds ratios for each group to risk ratios based on the estimated lifetime risk of prostate cancer. Because the base-case model represents the “average patient,” not necessarily a patient with negative family history and 11 risk alleles, we calibrated the model to correspond to the absolute risk estimates reported by Xu et al.¹⁰

Sensitivity Analyses

We developed a probabilistic cost-effectiveness model that allowed us to vary all model parameters simultaneously for 1000 Monte Carlo simulations according to assigned distributions (Table 1). These simulations provided the distributions for derivation of 95% confidence intervals (CIs).

We also evaluated the impact of individual model parameters and assumptions. First, we evaluated the impact of applying greater risks of high- and intermediate-grade cancers with finasteride (Table 1). We then varied the starting age for chemoprevention, the duration of chemoprevention, the absence of a beneficial effect of finasteride on BPH, disutilities associated with BPH and chemoprevention, and the costs of chemoprevention and treatment of prostate cancer. We also doubled the age-specific incidence of prostate cancer to reflect the increase in diagnoses that occurs with active screening.

Population-Level Analysis

To evaluate the cost-effectiveness of incorporating genetic testing into chemoprevention strategies, we applied the prevalence of family history and the distribution of the number of risk alleles based on the CAPS control group.¹⁰ We assumed that patients with positive family history for prostate cancer would receive chemoprevention without genetic testing. For patients with negative family history, we applied costs associated with genetic testing and varied the number of risk alleles beyond which patients would be targeted for chemoprevention. For comparison, we assumed patients with negative family history (without genetic testing) did not receive chemoprevention. We assumed total costs associated with genetic testing were \$400 per patient, but we also applied costs of \$200 and \$600 in sensitivity analyses.

Results

The lifetime risk of prostate cancer was 15.0%. The remaining lifetime risk among 50-year-old patients was 16.1%, the risk of biochemical recurrence was 4.7%, and the probability of death from prostate cancer was 1.7%. In the base-case analysis, chemoprevention reduced the risk of prostate cancer to 13.7% and the risk of death from prostate cancer to 1.3%. After discounting, the mean number of QALYs with chemoprevention was 17.963, a gain of 101.2 QALYs per 1000 patients (95% CI, 60.2–151.1). Discounted costs were \$13,957 per patient with chemoprevention, an incremental cost of \$9043 compared with patients not receiving

chemoprevention (95% CI, \$8549-\$9498). The resulting ICER was \$89,300 per QALY (\$58,800-\$149,800).

Positive family history and number of risk alleles significantly influenced the cost-effectiveness of chemoprevention with finasteride (Figure 2), ranging from \$43,400 per QALY (95% CI, \$29,400-\$76,100) for patients with positive family history and 14 or more risk alleles to \$128,600 per QALY (\$78,800-\$248,700) for patients with negative family history and 7 or fewer risk alleles. The ICERs for chemoprevention surpassed \$100,000 per QALY only for patients with negative family history and up to 11 risk alleles. The ICERs were approximately 36% lower for patients with positive family history across varying numbers of risk alleles.

Figure 3 shows the results from varying model parameters in 1-way sensitivity analyses. When we assumed finasteride increased the risk of higher-grade tumors, the ICER for chemoprevention increased to \$142,700 per QALY. The cost-effectiveness of chemoprevention with finasteride was sensitive to the utility weights assigned to BPH and finasteride. Compared with a utility of 0.95 (disutility, 0.05) for BPH in the base-case analysis, a utility of 0.90 reduced the ICER by 30%, and a utility of 1.0 (no disutility) increased the ICER by 77%. For patients receiving chemoprevention, even a utility decrement of 0.01 (instead of no disutility applied in the base case) resulted in fewer QALYs and higher costs, compared with patients not receiving chemoprevention.

When we incorporated risk and prevalence estimates from CAPS, the cost-effectiveness of chemoprevention was \$64,200 per QALY for patients with positive family history and \$101,000 per QALY for patients with negative family history (without genetic testing) (Table 2). Among patients with negative family history, estimated mean costs, including a \$400 genetic test, ranged from approximately \$5600 per patient with chemoprevention limited to patients with ≥ 14 risk alleles to approximately \$13,000 with chemoprevention expanded to patients with ≥ 8 risk alleles. In patients with negative family history, targeted chemoprevention increased costs and QALYs, but the ICERs varied little compared with chemoprevention in all patients with negative family history (Table 2). This result occurred because there was a balance between improved cost-effectiveness of chemoprevention in smaller groups of patients with more risk alleles and higher screening costs per patient initiating chemoprevention. The results were similar with genetic testing costs of \$200 or \$600 or estimates of risk and prevalence from the PLCO (data not shown).

Discussion

On average, a 1-year gain in quality-adjusted survival with finasteride chemoprevention would cost approximately \$90,000. However, cost-effectiveness can depend on the underlying risk in the target population.^{3,19,20} As the model revealed, family history and number of risk alleles are important factors in the cost-effectiveness of chemoprevention. Incremental cost-effectiveness ratios for chemoprevention were \$22,000 to \$45,000 per QALY lower (ie, more cost-effective) among men with positive family history, when holding constant the number of risk alleles. From another perspective, the cost-effectiveness of chemoprevention for men with negative family history and a higher number of risk alleles was similar to the cost-effectiveness for men with positive family history and a lower number of risk alleles. Thus, risk stratification based on family history alone is inadequate for efficient use of prostate cancer chemoprevention.

Although familial risk factors influence the cost-effectiveness of chemoprevention, comprehensive evaluation of the cost-effectiveness of chemoprevention on the basis of genetic information must include the cost of testing and the prevalence of inherited risk

alleles in the population. When we accounted for the distribution of risk alleles among patients with positive family history, the cost-effectiveness of chemoprevention was approximately \$64,000 per QALY. If this value is considered acceptable, genetic testing for patients with positive family history is simply cost-additive. Among patients with negative family history, the cost-effectiveness of adding a genetic test ranges from \$98,000 to \$103,000 per QALY with more and less restrictive strategies, respectively. The value of genetic testing would increase if future tests could better discriminate between low-risk and high-risk individuals or identify those most likely to benefit from chemoprevention.

We chose parameter estimates that were consistent with previous cost-effectiveness analyses.^{1–3} Svatek et al³ estimated a gain of 74 QALYs per 1000 patients with chemoprevention and the cost-effectiveness was \$122,700 per QALY. Zeliadt et al² estimated a gain of 46 QALYs per 1000 patients and incremental cost-effectiveness of \$200,000 per QALY. Both studies modeled an increase in the risk of high-grade cancers with finasteride. When we applied estimates of increased risks for higher-grade tumors and reduced risks for low-grade tumors in sensitivity analyses, we estimated a gain of 65.5 QALYs per 1000 patients and incremental cost-effectiveness of \$142,700 per QALY. Across the 3 independently developed models, estimated gains in QALYs are within 0.03 of each other (0.074–0.046).

The relatively small gain in QALYs from chemoprevention was sensitive to changes in utility weights assigned to BPH and chemoprevention. Svatek et al³ and Zeliadt et al² did not directly assign a disutility to finasteride. To maintain consistency, we also did not assign a disutility to chemoprevention in the base-case analysis. Svatek et al³ assumed that patients who experienced side effects such as erectile dysfunction with finasteride experienced reduced quality of life but discontinued the drug during the first year of treatment. This assumption limited the negative consequences of treatment on QALYs and costs. In our analysis, even with a disutility of 0.01 for finasteride, the direction of benefit changed, resulting in fewer QALYs with chemoprevention. This finding is notable considering that finasteride is associated with higher rates of erectile dysfunction, abnormal ejaculation, and breast enlargement than placebo.¹²

In addition, the impact of finasteride outside clinical trial settings is unclear. In PCPT, active surveillance for prostate cancer continued throughout the trial, so it is conceivable that the effect of finasteride could be attenuated among patients followed in routine practice. Cost-effectiveness analyses of human papillomavirus vaccine found that the benefits of the vaccine were eliminated with a 10% reduction in compliance with cervical cancer screening.²¹ It is also unclear whether the treatment effects measured in the PCPT apply equally to patients at higher risk for prostate cancer, whether treatment effects decline over time, and whether reductions in the prevalence of prostate cancer lead to declines in prostate cancer-specific mortality. Sixteen percent of men enrolled in the PCPT were not randomized because they had prostate-specific antigen levels greater than 3.0 ng/mL.¹² However, recent analyses have found that finasteride exerts a similar effect across quartiles of baseline levels of prostate-specific antigen.²²

There is no established threshold in the United States for determining whether an intervention is cost-effective. A \$50,000-per-QALY threshold emerged in the 1980s and was cited frequently during the subsequent decades. More recently, the literature has moved toward a threshold of \$100,000 per QALY.^{3,23} Although some commentators have argued that this threshold is still too low,²⁴ it is consistent with revealed-preferences studies on nonoccupational safety risks²⁵ and an empirical analysis suggesting that the threshold should approximate twice the annual income,²⁶ but it is higher than the threshold of £30,000 per QALY used in the United Kingdom.²⁷ Under the \$100,000 per QALY criterion, broad

use of chemoprevention with finasteride without risk stratification could be considered cost-effective based on point estimates from the base-case analysis. However, the associated CI extends well above \$100,000 per QALY, and sensitivity analyses revealed critical parameters that significantly influenced cost-effectiveness.

With genetically targeted chemoprevention, particularly among patients with negative family history, efficiency gains were limited from a cost-effectiveness perspective. Nevertheless, genetically targeted strategies can reduce overall expenditures associated with chemoprevention. If chemoprevention with finasteride were provided to all men aged 50 to 74 years,²⁸ total annual costs would exceed \$28 billion. However, if limited to men with positive family history, annual expenditures would approximate \$2.6 billion. At \$400 per patient, the total annual cost of genetic testing in all men with negative family history at age 50 years would be approximately \$800 million. This cost is small in comparison with potential savings ranging from \$2.8 billion to \$22.8 billion per year from limiting chemoprevention to higher-risk patients. Cumulative QALY gains from expanding chemoprevention to lower-risk groups does not keep pace with cumulative expenditures (Figure 4).

Conclusion

The cost-effectiveness of chemoprevention with finasteride is greatest among men with positive family history and higher numbers of inherited risk alleles. However, some of the gain in cost-effectiveness is offset by the use of genetically targeted chemoprevention, because this strategy requires genetic testing in all men who are candidates for chemoprevention with finasteride. From a cost perspective, genetically targeted strategies provide the opportunity to significantly reduce overall expenditures associated with chemoprevention.

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Abbreviations

BPH	benign prostatic hyperplasia
CAPS	Cancer of the Prostate in Sweden
CI	confidence interval
ICER	incremental cost-effectiveness ratio
PCPT	Prostate Cancer Prevention Trial
PLCO	Prostate, Lung, Colon, and Ovarian Cancer Screening Trial
QALY	quality-adjusted life-year

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Figure 1. Markov Diagram of Health States and Possible Transitions Among Them

Transition to death not attributable to prostate cancer may occur from any state (arrows not shown).

Figure 2. Incremental Cost-Effectiveness of Chemoprevention With Finasteride Across Strata Defined by Family History and Number of Risk Alleles

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Figure 3. One-Way Sensitivity Analyses

Abbreviations: BPH, benign prostatic hyperplasia; QALY, quality-adjusted life-year. The x-axis shows the incremental cost-effectiveness ratio (cost per quality-adjusted life-year); the y-axis shows the model parameters varied in 1-way sensitivity analyses. The single line extending beyond the x-axis represents an economically dominated scenario (ie, higher costs and fewer quality-adjusted life-years).

Figure 4. Cumulative Annual Expenditures and Quality-Adjusted Life-Years Gained With Chemoprevention

Abbreviation: QALY, quality-adjusted life-year.

Estimates assume that all patients with a given family history and a given number of risk alleles receive chemoprevention from ages 50 through 74 years. Patients aged 50 years with negative family history receive genetic testing at a cost of \$400 per patient. The annual cost of chemoprevention was \$771. Cumulative QALYs gained represent the difference between expected, discounted QALYs among patients receiving chemoprevention at age 50 years compared with men not receiving chemoprevention.

Table 1

Model Parameters and Base-Case Values

Model Parameter	Value (SE)	Distribution [*]	Source
Disutilities			
After prostatectomy		Beta	Stewart et al ²⁹
Gleason score 2 to 6	0.16 (0.02)		
Gleason score 7	0.19 (0.03)		
Gleason score 8 to 10	0.29 (0.03)		
Biochemical recurrence	0.33 (0.04)	Beta	Stewart et al ²⁹
Metastatic disease	0.75 (0.01)	Beta	Stewart et al ²⁹
Treated benign prostatic hyperplasia	0.05 (0.02)	Beta	Stewart et al ²⁹
Treatment with 5- α -reductase inhibitor	0	Beta	Assumption
Other parameter estimates			
Distribution of tumors without chemoprevention		Dirichlet	Thompson et al ¹²
Gleason score 2 to 6	0.707 (0.020)		
Gleason score 7	0.204 (0.018)		
Gleason score 8 to 10	0.089 (0.013)		
Relative risk of prostate cancer with finasteride		Log-normal	Thompson et al ¹²
All (base-case analysis)	0.752		
Gleason score 2 to 6	0.619		
Gleason score 7	1.230		
Gleason score 8 to 10	1.671		
Prevalence of benign prostatic hyperplasia requiring care		Beta	Bosch et al ¹⁶
Aged less than 75 years	0.15 (0.01)		
Aged 75 years and older	0.22 (0.01)		
Annual transition to biochemical recurrence		Beta	Svatek et al ¹ (from Kattan et al ¹⁴)
Gleason score 2 to 6	0.022 (0.006) [†]		
Gleason score 7	0.042 (0.012)		

Model Parameter	Value (SE)	Distribution [*]	Source
Gleason score 8 to 10	0.055 (0.032)		
Annual transition to metastatic disease	0.088 (0.016)	Beta	Pound et al ¹⁵
Annual mortality rate attributable to prostate cancer	0.188 (0.028)	Beta	Pound et al ¹⁵
Relative effect of 5- α -reductase inhibitor on benign prostatic hyperplasia	0.6	Log-normal	Thompson et al ¹²
Proportion of days of nonadherence with finasteride	0.147 (0.015) [‡]	Beta	Thompson et al ¹²
Costs			
Initial costs at 12 months after initial cancer diagnosis	\$12,774 (104)	Normal	Yabroff et al ^{17//}
Costs of terminal care for prostate cancer at 12 months	\$40,556 (262)	Normal	Yabroff et al ^{17//}
Annual costs for continuing cancer care	\$2569 (44)	Normal	Yabroff et al ^{17//}
Annual costs for treatment of benign prostatic hyperplasia	\$243	Fixed	Drugstore.com, August 28, 2009, doxazosin 4 mg daily
Annual costs for treatment of metastatic disease	\$2386	Fixed [§]	July 2009 average sales price, \$198.866 for 7.5 mg leuprolide, 12 injections per year
Annual costs for treatment of biochemical recurrence	\$2386	Fixed [§]	Assumption (same as metastatic disease)
Annual costs of chemoprevention	\$771	Fixed [§]	Drugstore.com, August 28, 2009, finasteride 5 mg daily

^{*} Distribution applied in probabilistic sensitivity analyses.

[‡] SE calculated using the sample size from Kattan et al¹⁴ (n = 983) and the distribution of Gleason scores from Stephenson et al.³⁰

[§] SE assumed to be equal to one tenth of the mean.

[§] Medication costs were not varied across Monte Carlo simulations.

// Costs updated to 2009 US dollars using the Consumer Price Index for medical care from the US Bureau of Labor Statistics.

Table 2
Results of Population-Based Analysis to Evaluate Cost-Effectiveness of Genetic Testing and Prevention Strategies

Group	No Chemoprevention		Chemoprevention		ICER
	Mean Costs	Mean QALYs	Mean Costs	Mean QALYs	
Positive family history*	\$7593	17.709	\$15,844	17.838	\$64,193
Negative family history*	\$4417	17.913	\$13,481	18.002	\$101,025
Negative family history and number of risk of alleles [†]					
≥ 14 risk alleles			\$5609	17.925	\$98,128
≥ 13 risk alleles			\$6440	17.934	\$92,822
≥ 12 risk alleles			\$7732	17.947	\$94,886
≥ 11 risk alleles			\$9249	17.962	\$98,030
≥ 10 risk alleles			\$10,722	17.976	\$99,844
≥ 9 risk alleles			\$11,847	17.986	\$101,117
≥ 8 risk alleles			\$12,848	17.994	\$103,213

Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

* Stratification based on family history alone does not require genetic testing. The cost of genetic testing was set to \$0 in the analysis.

[†] Stratification based on the number of risk alleles requires genetic testing. The cost of genetic testing was set to \$400 per patient in the analysis.

The incremental cost-effectiveness ratios are for (a) genetic testing for all patients with negative family history, chemoprevention for those with the given number of risk alleles, and no chemoprevention for those with less than the given number of risk alleles, compared with (b) no chemoprevention for any patient.