Influence of Perspective on Preferences for Prostate Cancer Outcomes

Katharine S. Gries

A dissertation

submitted in partial fulfillment of the

requirements for degree of

Doctor of Philosophy

University of Washington

2014

Reading Committee:

Donald L. Patrick, Chair

Scott D. Ramsey

Dean A. Regier

Program Authorized to Offer Degree:

School of Pharmacy

University of Washington

Abstract

Influence of Perspective on Preference for Prostate Cancer Outcomes

Katharine S. Gries

Chair of the Supervisory Committee:

Professor Donald L. Patrick

Department of Pharmacy

Background

The utility value is a necessary component of the cost-utility analysis (CUA). They can be obtained from various perspectives and using different methods. The relationship between elicitation methods and perspectives is unknown in prostate cancer.

Objective

To quantify the difference in utility values comparing three different perspectives and disease-specific health states with a generic preference measure. Then to understand the sensitivity of the disease-specific utility value derived from three perspectives in a CUA model.

Methods

Disease-specific health states were developed with attributes that varied across five health domains: sexual function, urinary function, bowel function, pain, and emotional well-being. Men with prostate cancer, men at risk for prostate cancer, and a sample from the general population were recruited to value the health states using standard gamble (SG) methodology and to complete the Health Utilities Index (HUI). Disease-specific utility values were modeled in a prostate cancer CUA to assess the sensitivity of the parameter estimate.

Results

136 participants (n= 43 prostate cancer; n=40 at risk, n=49 general population) completed the study visit. Mean disease-specific utility values ranged from 0.46 to 0.85 for men with prostate cancer, 0.37 to 0.75 for men at risk, and 0.32 to 0.81 for the general population group. Mean HUI3 current health ratings: men with prostate cancer HUI3: 0.75 (SD=0.260), men at risk HUI3: 0.77 (SD=0.238), general population HUI3: 0.84 (SD=0.178). There were small differences in utility values comparing between perspectives and between the SG and HUI methods. While the incremental cost-effectiveness ratios were high and would not be considered cost-effective, using the perspective of the general population was more cost effective compared to the patient perspective.

Conclusion

The utility values for men with prostate cancer support the hypothesis that patients experiencing the disease state (patient perspective) assign higher utility values to disease-specific health states. Utility values were higher when obtained by the generic, preference based measure compared to the disease-specific method. The CUA was sensitive to the change in utility value when holding all other parameters constant.

Table of Contents

List of Tables

List of Figures

Introduction

Health related quality of life (HRQoL) is one aspect of quality of life and focuses on physical functioning, emotional functioning and social functioning [1]. In the context of health care, HRQoL contributes to selection of treatments. The selection of treatment options based on HRQoL is especially important in situations where the intervention does not improve life expectancy but could potentially improve or decrease quality of health. A health state is a written description of HRQoL attributes including presence, frequency, intensity of symptoms, abilities, and feelings. These health states can then be used to measure individuals' well-being or satisfaction using preference-based approaches [1]. The value assigned to the attributes and levels included in the health state are used in health economics research, cost-effectiveness modeling, and evidence based medicine.

Health state valuations also referred to as preference weights or utility values are necessary components of cost-utility assessments and calculation of quality adjusted life years (QALY). Cost-utility analysis (CUA) is a type of cost-effectiveness analysis in which health effects are measured in terms of QALY gained. QALY represents the duration of an individual's life accounting for changes in the quality of health over time [2]. The cost-utility model generates an incremental cost-effectiveness ratio (ICER) to quantify the additional cost per extra unit of effect (QALY) comparing one intervention to another. The sensitivity of the ICER estimate depends heavily on the accuracy of the model inputs, including the utility value. Accuracy of the utility value depends on the use of the appropriate perspective and selection of the appropriate method for measuring utility based on the study objective.

The evaluation of health states can be conducted from various perspectives; including, the patient perspective or the societal perspective. Welfare economic theory supports the perspective of the health state affected person as the preferred source whereas extra-welfarist theory supports a generic and community based preference to allow for comparison of preferences across disease categories and for use in the decision of allocation of limited recourses [3]. The extra-welfarist believes that the post-illness preferences would too often result in the provision of marginally beneficial care and are subject to change and adaptation [4]. Political differences and the scientific questions or context of use can influence the preferred perspective of choice. Given the strengths, limitations, and biases of both the patient and societal perspectives, understanding the difference and the consequence of selection on decision-making warrants further investigation.

Rationale

Policymakers may allocate scarce resources on the basis of a CUA, so it is important that the values obtained for these assessments are consistent for comparison purposes [5]. A study assessing well-being in patients with dialysis aimed to address the difference in cost-effectiveness analysis using different preference measures: Sickness Impact Profile, Campbell Index of Well-Being, Standard Gamble, Time Trade-off, Categorical Scaling, and the Kaplan-Bush Index of Well-Being [5]. The Sickness Impact Profile produced the lowest cost/QALY at $34,893 and the standard gamble produced highest at $45,254 for the other indices the time trade off was $39,338, categorical scaling $41,095, Campbell Index $43,048, and Kaplan-Bush Index $43,952 [5]. As demonstrated in this example, the cost-effectiveness analysis was sensitive to the measure chosen to elicit the utility parameter. This is particularly important for treatments that are close to the reimbursement threshold. Decision makers gain greater confidence in the evaluation of controversial or costly technologies by conducting sensitivity analyses with multiple preference inputs [5]. Two studies examined sensitivity of ICER with differences in utility estimates [6, 7]. The adjustment of the utility parameter caused estimates to cross thresholds for dominance of $50,000 or $100,000 in 18% of cases [6]. The sensitivity analysis demonstrated similar findings: in 31% of the cases the ICER exceeded a threshold and in 13% of the cases the ICER fell below a threshold [7]. The sensitivity of the preference estimates in a CUA could have major implications for funding decisions [8].

Prostate cancer can present as symptomatic or asymptomatic, and symptoms are uncommon in men with local disease. Possible symptoms in more advanced stages include changes in urinary, bowel and/or sexual function; such as, the need to urinate frequently, difficulty with urination, painful urination, and difficulty with an erection, painful erection, blood in urine, and pain or stiffness in lower back [9]. With advancements and increase in prostate specific antigen (PSA) screening, diagnosis in the early, asymptomatic stages is increasing and more cases are being detected [10]. HRQoL considerations play an important role in prostate cancer given the long duration of life, occurrence of symptoms, and potentially serious side effects from treatment. The effect of perspective on preference has been explored in schizophrenia, breast cancer, colorectal cancer, head and neck cancer, but not prostate cancer [11].

This study aims to demonstrate how perspective influences utility value, how method of elicitation influences utility value, and the sensitivity of utility value on the ICER in a CUA for prostate cancer. The three different populations to address the research questions are: patient perspective, societal perspective, and a population at-risk for the disease state. The two different methods are: disease-specific health states and a generic measure based on community preferences. This research highlights the importance in choosing between different preference elicitation methods and using different perspectives when measuring utility estimates for prostate cancer cost-utility models.

Objective

The objective of this research study was to quantify the difference in utility values comparing three different perspectives and disease-specific health states with a generic measure based on community preferences in the context of prostate cancer. Then to understand the sensitivity of the utility values derived from the patient perspective, the societal perspective, and an at-risk perspective in a prostate cancer CUA model. This study adds to the body of literature by measuring preferences in patients with prostate cancer, men at risk for prostate cancer, and the general population using the same preference elicitation methods and study design.

Specific Aims

- Measure utility values for the patient perspective, an at-risk population, and the societal perspective for disease specific (prostate cancer) health states and using a generic preference measure.

- Develop an algorithm to calculate utility values based on the disease-specific health state classification system and compare the algorithm for the three different perspectives.

- Apply the disease-specific utility values to a cost-utility model and explore the sensitivity of the utility value when using the three different perspectives: patient perspective, at-risk population perspective, and the societal perspective.

Literature Review to Inform Research Question

Objective

A literature review was conducted to determine the extent that preferences or utility values have been collected in men with prostate cancer and to understand the preference elicitation method and study populations. To understand the landscape of methodological considerations in preference elicitation studies a review was conducted to determine if the difference in preference value between study populations or between elicitations methods has been conducted in any therapeutic area. Results from this literature review informed the development of the proposed research study and the merit in conducting a study to examine the difference in preference value comparing between study populations and between elicitation methods for prostate cancer outcomes.

Methods

A targeted literature review was conducted in PubMed, focusing on review articles that (1) report preference values for men with prostate cancer using a direction elicitation method and (2) report on preference values that compare the patient perspective to alternative perspectives and compare between elicitation methods for any disease state. For the studies reporting preference values for men with prostate cancer, data was extracted on the study population, sample size, elicitation method, and the preference value. For studies comparing preference value between population data was extracted on the therapeutic area, study population, elicitation method, and the preference value.

Results

Search 1: Preference values for prostate cancer outcomes for similar health state attributes varied greatly based on method for elicitation, study population, various context effects, and mode of presentation [Table 1]. These inconsistencies greatly limit the ability to compare results without understanding the context of the study, participants, and data collection. Time trade off (TTO) was the most frequently used disease-specific preference elicitation method. The TTO utility values were higher compared to preferences derived from standard gamble methodology (SG) [12]. Patients rating their own health reported higher utility compared to non-patients rating scenarios and higher utility than patients rating scenarios [12]. Notable differences in study design included the following variables: regional representation, health state components, and participant population. The populations in the review included oncologist/urologist, healthy men, and patients with prostate cancer (positive/negative biopsy, with symptoms, local/metastatic disease, and pooled patients with unknown characteristics). The variability in participants/perspectives limits comparison across studies and is a possible source for the range in preference values. The review highlighted diversity in preference values and a lack of consistency in valuation of prostate cancer outcomes.

Search 2: The effect of post-illness influence on the valuation of health found no unequivocal conclusion on the preferred preference elicitation method or perspective across studies [Table 2]. The therapeutic area in this review ranged from oncology (breast cancer, colorectal cancer, head and neck cancer), psychiatric disorders (schizophrenia), seriously ill/ICU patients, dialysis, stroke, and Gaucher disease. The perspectives included: healthy people, patients, clinicians, and caregivers. In general, people experiencing the health state provided higher utility for that health state compared to those who do not experience the health state [11].

The exceptions included 2 studies using the EQ-5D; the investigators found agreement in estimates between seriously ill patients and healthy volunteers and stroke patients and caregivers [13, 14]. In Gaucher disease (GD), healthy participants and patients with chronic disease, not GD, had higher estimates compared to patients with GD [15]. In breast cancer, investigators found no significant difference in preference between women with breast cancer and men [16]. Generic preferences measures, such as the EQ-5D, behave differently than direct preference elicitation methods such as TTO and SG, and TTO and SG produce different preference estimates [11]. The differences between the TTO and SG are expected given the different theoretical grounds, estimation methods and assumptions [17].

Conclusion

While these reviews highlight the difference in utility values based on both the type of measure and the perspective, there is a gap in determining the magnitude of difference within the context of prostate cancer and the implications of the different estimates on decision-making in healthcare.

Literature Review to Inform Development of Health States

Objective

The purpose of the literature review was to identify health state attributes relevant to men with prostate cancer and appropriate for use in a preference elicitation study.

Methods

To determine the most appropriate prostate cancer outcomes for use as health state attributes three different sources of information were reviewed: (1) previously developed patient reported outcome (PRO) measures in prostate cancer, generic PRO measures validated in patients with prostate cancer, and previous health states used for prostate cancer preference elicitation measures, (2) qualitative research conducted in patients with prostate cancer, and (3) a review of an online patient forum to gain an understanding of the most commonly reported symptoms from patients with prostate cancer.

Sources for Search 1 (PRO measures) and Search 2 (qualitative research) were obtained by reviewing the literature in PubMed. Search 3 (online forum) was conducted through the use of PatientsLikeMe.com, an online forum for men with prostate cancer to common symptoms and discuss their disease with other men with prostate cancer.

Results

Search 1: Prostate Cancer PRO Measures and Generic Measures Validated in Men with Prostate Cancer

PRO measures for prostate cancer or measures validated in men with prostate cancer were the UCLA – PCI (University of California Los Angeles – Prostate Cancer Index), EPIC (Expanded Prostate Cancer Index Composite), FACT-P (Functional Assessment of Cancer

Therapy), EQ-5D, SF-36, HUI, and PORPUS (Patient-Oriented Prostate Utility Scale). Attributes identified from these measures included: urinary function, urinary bother, bowel function, bowel bother, sexual function, sexual bother, hormonal function, hormonal bother, physical well-being, social well-being, emotional well-being, functional well-being, pain, appetite, energy, communication with doctor, support, and general health perceptions [Table 3].

Search 2: Qualitative Research in Men with Prostate Cancer

The qualitative research literature supports similar concepts, inclusive of: impaired urinary control, urinary incontinence, bowel problems, reduced libido, intimacy issues, erectile dysfunction, hormonal alterations, anxiety, worry, depression, pain, fatigue, uncertainty, support from others, and confidence in healthcare team [Table 3].

One on one interviews were conducted in 10 patients with prostate cancer to identify themes of the lived experience [18]. Themes were: living in the unknown, yearning to understand and know, struggling with unreliability of body, bearing the diagnosis of cancer, shifting priorities in the gap, and feeling comfort in the presence of others. Interviews were conducted in men after 2 years of prostate cancer diagnosis [19]. All of the men stated they experience every day fatigue. There were mixed responses in regards to living with uncertainty and trust in the physician and the information being provided to them. Over the two years, there is an increase in self-esteem and confidence. The men begin to engage themselves prostate cancer education, attitudes are altered, and they report not dwelling on the change in sexual activity and desire. Men without partners were interviewed to determine how they make decisions about prostate cancer treatment, manage side effects, and obtain information and support [20]. The following themes were raised during the 20 interviews: going it alone, diagnosis and treatment decision making, sources of information and support, the aftermath of prostate cancer, and coping strategies. The role of the healthcare team varied between men; however, these men often chose the treatment their physician suggested. The aftermath of treatment and dealing with the adverse effects, including bowel, sexual and urinary problems resonated among the study participants. An important means of coping was having confidence in the healthcare team.

Experiences of men with prostate cancer after radical prostatectomy were elicited by conducting 10 interviews [21]. During the 10 interviews, there was a strong response of having sexuality called into question and feeling powerless because of their urinary incontinence. This was described as a “leaking body.” These experiences with urinary incontinence and erectile dysfunction generated fear or disappointing others. Participants felt as if their body had become limited and finite. The investigators summarize the following key points; urinary continence and erectile function have strong symbolic elements associated with masculinity and urinary incontinence and erectile dysfunction following radical prostatectomy can precipitate a sense of failure in men, resulting in anxiety and depression. Focus groups with patients with prostate cancer and their spouse/caregiver were conducted to probe on the symptoms of prostate cancer, ability to manage the symptoms, and perceptions on interventions that would manage the symptoms [22]. The researchers identified four major themes: enduring uncertainty, living with treatment effects, coping with changes, and needing help. As part of living with treatment effects, the focus group participants discussed the experience of losing urinary control, sexual difficulties, hormonal alterations, and overwhelming fatigue.

A systematic literature review was conducted to understand the knowledge and perceptions of prostate cancer among Black men [23]. The focus is on understanding barriers to prostate cancer screening for those who do not have prostate cancer, but I have decided to include this review since it paints the picture as to what concepts are important for men in perceiving their risk of prostate cancer. Individual factors include: knowledge of the prostate gland, prostate cancer symptoms and prostate cancer risk, knowledge about diagnostic tests and treatment, patient-provider communication, and perception of personal risk. Concerning prostate cancer treatments, man feared pain, reduced libido, and impaired urinary control. The sociocultural factors include: threat to masculine identity, fear of cancer, mistrust of health care system, and culturally specific information.

Search 3: Review of Patient Symptoms Reported on the Online Forum

The online forum, patientslikeme.com, allows patients with prostate cancer an opportunity to discuss their symptoms and experiences. The forum summaries data on the symptoms reported by disease area and provides this data for researches. The top 5 symptoms reported from patients with prostate cancer included: depressed mood, fatigue, insomnia, pain, and anxious mood [Table 3].

Conclusion

From the list of potential attributes; five were selected based on the following criteria: frequency of attribute reported in the literature, the most common symptoms reported on the patient forum, and feasibility of including the attribute in a preference elicitation study based on the opinion of the study team. The prostate specific attributes in the health states were: urinary function, bowel function, sexual function, emotional well-being, and pain.

Study Population

Participants from four counties in the western Washington region (King, Kitsap, Pierce, and Snohomish) were invited to participate in the study. To be eligible for the study, participants had to meet the inclusion criteria for one of the three study groups: men with prostate cancer, men at risk for prostate cancer, or a representative sample of the general population. Each study group had a different sampling frame, described below. In addition to the eligibility criteria, study participants had to be able to understand and complete the interview in English; attend the study visit in person either at a University of Washington campus or the Fred Hutchinson Cancer Research Center; and willing and able to given written informed consent. The study protocol and consent form were submitted and approved by the FHCRC and the UW institutional review board. The descriptive characteristics of the study population, by group, are presented in Table 4 and the comorbid conditions, reported by the study participants, are presented in Table 5. The pooled sample includes 4 participants (men with prostate cancer) who were eligible at the time of screening, but turned 71 years old before their study visit. The participants were not included in the study group statistical analyses.

Men with Prostate Cancer

Men with prostate cancer were recruited from the Cancer Surveillance System (CSS), at the Fred Hutchinson Cancer Research Center (FHCRC). The CSS is part of the Surveillance, Epidemiology, and End Results (SEER) program and provides data to the Washington State Cancer Registry. Eligible participants were between 45 to 70 years of age; had a histological confirmed diagnosis of prostate cancer within the past 3 years; and self-report experience with prostate cancer symptoms at the time of screening.

Men at Risk for Prostate Cancer

Men at risk for prostate cancer were recruited from the University of Washington Medical Center (UWMC) urology clinic and the prostate oncology center. Eligible participants were 45 to 70 years of age; had elevated prostate specific antigen (PSA $\geq$ 2.6 ng/mL); and no prostate cancer specific symptoms at the time of screening.

General Population

The general population was recruited from the Washington State Department of Licensing Database. Eligible participants were 18 to 70 years of age and no diagnosis of prostate cancer. The general population group included both men and women and adults younger than 45 years old. The intention was to create a sample representative of the societal perspective which includes women and young adults.

Response Rate

Figure 1 shows the disposition of the study sample, including the number of participants approached to reach the desired sample size. Overall 650 people were invited to participate in the study (20.3% response rate), with response rates differing in each group. For men at risk for prostate cancer group the response rate was 78.4%; only men eligible for the study and provided consent with the urology clinic to be contacted about studies were approached. The response rate in the men with prostate cancer group was 21.6%; using the recruitment strategy of random letter mailings the sample was pre-screened for eligibility and cancer patients in the SEER registry are savvy to clinical trials and familiar with the value of research. Use of the Washington State Department of Licensing database produced a response rate of 12.3%; increased by some incidental snow-ball sampling as participants in the study shared the approach letter with others.

Study Measures

Study participants completed one in-person study visit. During the visit they used a visual analog scale (VAS) to rank the health states, completed the standard gamble (SG) interview using a change board, and completed the Health Utilities Index (HUI) and a sociodemographic form. The same interviewer conducted all of the study visits ensuring that the visits were consisted and the participants understood the study activities.

Visual Analog Scale

The VAS exercise was conducted to introduce the participants to the health states. Participants rated each health state from worst imaginable health (0 = dead) and best imaginable health (100 = full health). The participant was permitted to alter ratings until satisfied that the relative and absolute rankings reflected his/her preferences as accurately as possible.

Standard Gamble

Participants completed the SG task with time horizon 'the rest of your life.' Participants were presented with a health state and offered a choice between two alternatives, one that is certain and one that is uncertain. Choice A was the uncertain choice and contained two health state outcomes; to remain in full health "for the rest of your life" with a probability of p or death with a probability of $1 - p$. Choice B was to remain in the target health state "for the rest of your life". Probability p was then varied, by increments of 10% until the participant was indifferent between choices A and B [24].

The health states included five attributes (sexual function, urinary function, bowel function, pain, and fear of the future) each with three levels ranging from never/no to always/considerable [Table 6]. The descriptive system includes 243 health states, far too many for the sample to evaluate. A total of 18 health states were selected using an orthogonal experimental design. Each participant was randomly assigned to one of the three health state sets and valued a total of 6 health states. A sample health state card is shown below.

Sample of a Health State Card

For the Rest of Your Life
You never experience problems with achieving and maintaining an erection
You never experience problems with urination
You never experience problems with diarrhea and / or constipation
You experience severe pain that limits your activities
You experience considerable fear of the future

Health Utilities Index

The HUI is a generic preference measure based on community preferences to derive multi-attribute utility values. Participants completed the HUI 15-item questionnaire for self-assessed “usual” health status assessment, a generic preference-based measure [25, 26]. The self-administered HUI 15-item questionnaire for self-assessed “usual” health status assessment was used to score both the HUI mark 2 (HUI2) multi-attribute utility function and the HUI mark 3 (HUI3) multi-attribute utility function. The HUI2 includes 7 single attribute utility functions: sensation, mobility, emotion, cognition, self-care, pain, and fertility. The HUI3 includes 8 single attribute utility functions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each single attribute utility scale is defined such that full function has a single attribute utility score of 1.00, and the lowest functional level (most disabled) for that attribute has a single attribute utility score of 0.00.

Table 1. Preference Values for Men with Prostate Cancer

Reference	Study population	Sample size	Preference Elicitation Method	Results
Singer [27]	Men without prostate cancer	50 men	TTO	Median survival traded to maintain sexual functioning: 0.5 years (range 0 to 4)
Bennett [28]	Prostate cancer patients Physicians	27 patients: localized prostate cancer 17 patients: metastatic prostate cancer. 43 physicians	TTO	Stable: physicians 0.92, localized 0.88, metastatic 0.78. Early progression: physicians 0.83, localized 0.53, metastatic 0.58. Late progression: physicians 0.42, localized 0.05, metastatic 0.05.
Matchar [29]	Physicians	43 physicians	TTO	Asymptomatic (stable): 0.917 Early progression: 0.833 Late progression: 0.417
Volk [30]	Healthy subjects	168 couples	TTO	Husbands reported lower utilities than did their wives
Albertsen [31]	Newly diagnosed patients with localized prostate cancer	50 men	TTO HUI-3	Overall health: 0.91 Overall problems related to prostate cancer: 0.92 Urinary problems: 0.89 Bowel problems: 0.98 Sexual dysfunction:0.90 HUI-3: 0.917
Chapman [32]	Men with prostate cancer	59 patients	TTO	High 0.78, moderate 0.72, low 0.35, current 0.83
Chapman [33]	Men with localized or metastatic prostate cancer	57 men	TTO	Health state A (least severe): 0.84, health state B: 0.66, health state C (most severe): 0.23. Personal state: 0.79.
Souchek [34]	Males with advanced prostate cancer	120 men	TTO SG Rating Scale	Time trade off was consistently higher than rating scale and standard gamble.

Saigal [35]	Male patients with elevated PSA	214 men	TTO	Urinary function 1.0; sexual function 0.99; bowel function 0.99; urinary incontinence 0.99; erectile dysfunction 0.98; radiation proctitis 0.83.
Smith [36]	Men with prostate cancer	209 men	TTO SG	Time trade off: Urinary and sexual dysfunction (0.676 ± 0.310), Sexual but not urinary dysfunction (0.869 ± 0.209), no sexual or urinary dysfunction (0.923 ± 0.205). Standard gamble: Urinary and sexual dysfunction 0.822, sexual but not urinary dysfunction 0.898, no sexual or urinary dysfunction 0.956
Bhatnagar [37]	Men with and without prostate cancer	162 men	SG	Sexual dysfunction: 0.89 Urinary symptoms: 0.87 Bowel dysfunction: 0.45
Elkin [38]	Men without prostate cancer	63 men	TTO	Time trade off: watchful waiting: 0.72 hormonally responsive metastatic cancer: 0.47 hormonally refractive metastatic cancer: 0.19 treatment-related incontinence: 0.62 Treatment related impotence: 0.71
Elstein [39]	Patients with newly diagnosed localized prostate	120 patients and their clinicians	TTO	Patients: Health state A (best state): 0.76, health state B: 0.51, health state C (worst state): 0.31, current state: 0.73 (SD 0.25). Clinicians: Health state A (best state): 0.91, health state B: 0.75, health state C (worst state): 0.47, current state: 0.82 (SD 0.20).

Table 2. Preference Studies Comparing Population and Elicitation Method

Reference	Therapeutic area	Study population	Elicitation method	Results
Sackett [40]	Dialysis	Healthy individuals and home dialysis patients	TTO	Home dialysis patients place higher utility on treatment states for renal failure compared to healthy individuals.
Boyd [41]	Patients with colostomy	Surgeons and oncologist, rectal cancer patients with colostomy, rectal cancer patients without colostomy, healthy volunteers, university students	SG	The highest utility values were from patients with colostomy and the lowest was from university students and patients without colostomy.
Hall [42]	Breast cancer	Women with breast cancer, women without breast cancer.	TTO	There were significant differences in the utilities across age groups and between breast cancer and non-cancer respondents.
Ashby [16]	Breast cancer	Nurses, hospital doctors, general practitioners, university staff, breast cancer patients	TTO	The personal experiences of breast cancer patients resulted in higher values for 'good' psychosocial scenarios compared to those with no direct experience. Differences did not reach significance in comparison between breast cancer patients and males.
Tsevat [43]	Seriously ill patients	Seriously ill patients, the patients decision maker, and the patient’s physician.	TTO	The patient utility was higher than surrogate utility. Patients gave higher ratings to their state of health than did physicians.
Badia [13]	ICU patients	Healthy individuals, and ICU patients	EQ-5D	Moderate to good agreement between patients and proxy pairs was observed in physical areas and pain/discomfort and there was fair agreement for anxiety/depression.

Revicki [44]	Schizophrenia	Patients with schizophrenia, caregivers, psychiatrists	Rating scales	Correlations between the physician-rated, patient-rated, and caregiver-rated were uniformly high. Psychiatrists and caregiver correlations were weak.
Clarke [15]	Gaucher disease	Healthy participants, patients, patients with chronic diseases but not Gaucher disease	TTO SG	The utilities elicited by TTO and SG differ between populations for at least two of the health state descriptions.
Dominitz [45]	Colorectal cancer	Patients, patients undergoing screening, patients participating in a screening study, patients who had never undergone screening	TTO	Unscreened patients were willing to trade significantly more time to avoid colonoscopy with perforation than were either patients volunteering for colonoscopic screening or colorectal cancer patients
Dorman [14]	Stroke	Patients and proxy	EQ-5D	Mean HRQoL for patients was 64.2 and for proxy was 62.0.
Molzahn [46]	Dialysis and transplant	Nurses, physicians, and patients	TTO	Low to moderate correlations between nurses and patients, and physicians and patients. Moderate correlation between nurses and physicians.
Jalukar [47]	Head and neck cancer	Patients, physicians, and students	TTO	Health-care professionals and patients have very similar attitudes regarding the desirability of potential health-state outcomes. Health care professionals and patients had significantly different rankings than students.
Tsevat [48]	Hospitalized patients	Patients and their surrogates	TTO	The correlation between patients' and their paired surrogates' health values was modest.

Table 3. Health State Attribute Tracking Grid

PRO instruments	**PORPUS**	Symptoms from online forum	Qualitative studies
Urinary function, urinary bother	Urinary frequency/ leaking urine/ poor bladder control		Impaired urinary control; losing urinary control; urinary incontinence
Bowel function, bowel bother	Bowel problems		Bowel problems
Sexual function, sexual bother	Sexual function, Sexual drive/interest		Sexual function; reduced libido; Sexual dysfunction; Intimacy issues; Sexual problems; Erectile dysfunction
Hormonal function, hormonal bother			Hormonal alterations
Physical well-being			
Social well-being			
Emotional well-being		Depression/anxiety	Anxiety; Worry; Depression; Uncertainty in life expectancy and in treatments
Functional well-being			
Pain	Pain and disturbing body sensations	Pain	Distressing comfort; Pain
Appetite			
Energy	Energy	Fatigue	Fatigue
Communication with doctor	Communication with doctor		Trusted connection; patient-provider communication; Confidence in healthcare team
General health perceptions			
	Support from family and friends		Support; sharing with others and drawing together; needing help
		Insomnia	

Table 4. Demographic Characteristics of the Study Group

Characteristic	Pooled Sample (n=136)	At Risk for Prostate Cancer (n=40)	Men with Prostate Cancer (n=43)	General Population (n=49)
Age (years) Mean (SD)	55.5 (13.45)	60.2 (5.97)	63.4 (5.46)	43.2 (14.09)
Median [range]	59 [20-73]	60 [47-70]	65 [49-71]	41 [20-70]
Male, n (%)	108 (79.4%)	40 (100.0%)	43 (100.0%)	21 (42.8%)
Race				
African American	8 (5.9%)	3 (7.5%)	2 (4.6%)	3 (6.1%)
Asian	6 (4.4%)	1 (2.5%)	0	5 (10.2%)
Caucasian	108 (79.4%)	31 (77.5%)	39 (90.8%)	34 (69.5%)
Hispanic	3 (2.2%)	2 (5.0%)	0	1 (2.0%)
Pacific Islander	1 (0.7%)	0	0	1 (2.0%)
Other	10 (7.4%)	3 (7.5%)	2 (4.6%)	5 (10.2%)
Employment				
Full time or part time work	71 (52.2%)	20 (50.0%)	15 (34.9%)	35 (71.4%)
Retired	45 (33.1%)	14 (35.0%)	23 (53.5%)	7 (14.4%)
Disabled	5 (3.7%)	2 (5.0%)	0	3 (6.1%)
Unemployed	4 (2.9%)	0	1 (2.3%)	3 (6.1%)
Other	11 (8.1%)	4 (10.0%)	4 (9.3%)	1 (2.0%)
Education				
High school	16 (11.8%)	5 (12.5%)	5 (11.6%)	6 (12.2%)
Some college	37 (27.2%)	13 (32.5%)	11 (25.6%)	12 (24.5%)
College degree	46 (33.8%)	13 (32.5%)	19 (44.2%)	13 (26.5%)
Post-graduate degree	37 (27.2%)	9 (22.5%)	8 (18.6%)	18 (36.8%)
Living Condition				
Live alone	46 (33.8%)	16 (40.0%)	5 (11.6%)	24 (49.0%)
Live with someone	85 (62.5%)	24 (60.0%)	38 (88.4%)	23 (46.9%)
Relationship Status				
Single	31 (22.8%)	8 (20.0%)	3 (7.0%)	20 (40.8%)
Married	80 (58.9%)	24 (60.0%)	38 (88.4%)	16 (32.7%)
Divorced	20 (14.7%)	5 (12.5%)	1 (2.3%)	12 (24.5%)
Widowed	4 (2.9%)	3 (7.5%)	0	1 (2.0%)
Have Children n (%)	84 (61.8%)	14 (35.0%)	34 (79.1%)	20 (40.8%)
Religious n (%)	67 (49.3%)	25 (62.5%)	20 (46.5%)	20 (40.8%)
Trusting Relationship with Physician n (%)	125 (91.9%)	38 (95.0%)	43 (100.0%)	40 (81.6%)

Table 5. Comorbidites by Study Group

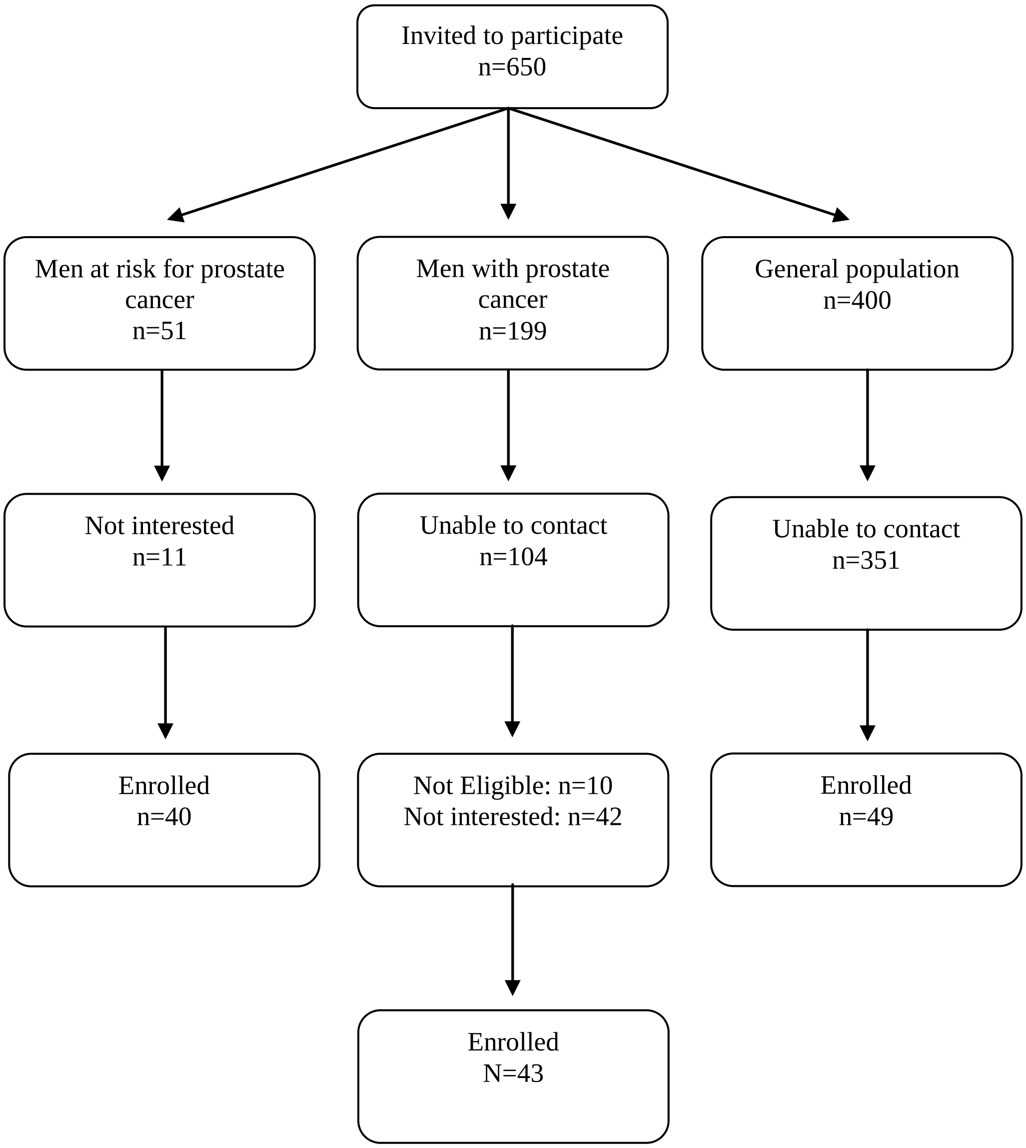
Characteristic	Men with Elevated PSA (n=40)	Men with Prostate Cancer (n=43)	General Population (n=49)
Number of Comorbid Conditions			
0	10 (25.0%)	0	25 (51.0%)
1	11 (27.5%)	14 (32.6%)	13 (26.5%)
2	12 (30.0%)	10 (23.3%)	4 (8.2%)
3	4 (10.0%)	15 (34.9%)	6 (12.2%)
4	0	0	1 (2.0%)
5	3 (7.5%)	3 (7.0%)	0
6	0	2 (4.6%)	0
Type of Comorbid Condition			
Cancer	4 (10.0%)	43 (100.0%)	3 (6.1%)
Hypertension	9 (22.5%)	16 (37.2%)	7 (14.3%)
Arthritis	11 (27.5%)	15 (34.9%)	7 (14.3%)
Depression	9 (22.5%)	5 (11.6%)	4 (8.2%)
Diabetes	5 (12.5%)	6 (13.9%)	0
Heart Attack or Heart Disease	6 (15.05%)	2 (4.6%)	1 (2.0%)
Stroke	0	2 (4.6%)	1 (2.0%)
Angina	0	1 (2.3%)	1 (2.0%)
COPD	0	0	1 (2.0%)
Other Mental Health Condition	3 (7.5%)	1 (2.3%)	2 (4.1%)
Other Health Condition	10 (25.0%)	9 (20.9%)	12 (24.5%)

Participants allowed to select more than one condition; not mutually exclusive

Table 6. Health State Dimensions and Levels

Dimension	Level	Numeric Score
Sexual Function	Never experience problems with achieving and maintaining an erection	1
	Sometimes experience problems with achieving and maintaining an erection	2
	Always experience problems with achieving and maintaining an erection	3
Urinary Function	Never experience problems with urination	1
	Sometimes experience problems with urination	2
	Always experience problems with urination	3
Bowel Function	Never experience problems with diarrhea and/or constipation	1
	Sometimes experience problems with diarrhea and/or constipation	2
	Always experience problems with diarrhea and/or constipation	3
Pain	No pain that limits your activities	1
	Moderate pain that limits your activities	2
	Severe pain that limits your activities	3
Fear of the Future	No fear of the future	1
	Minimal fear of the future	2
	Considerable fear of the future	3

Figure 1. Disposition of Study Sample



Chapter I: Preferences for Prostate Cancer Outcomes: A comparison of the patient perspective, general population perspective, and a population at risk for prostate cancer

Abstract

Objective: To compare utility values derived from two different preference elicitation methods and across different study populations for prostate cancer.

Methods: Prostate cancer specific health states were developed with attributes that varied across five health domains: sexual function, urinary function, bowel function, pain, and emotional well-being. Men with prostate cancer, men at risk for prostate cancer, and a sample of the general population assigned value to 18 health states using standard gamble (SG) methodology. Study participants also completed the Health Utilities Index (HUI) to obtain utility values using a generic community weighted preference measure.

Results: 136 participants were enrolled (n= 43 prostate cancer; n=40 at risk, n=49 general population). Mean HUI3 current health ratings: men with prostate cancer HUI3: 0.75 (SD=0.260), men at risk HUI3: 0.77 (SD=0.238), general population HUI3: 0.84 (SD=0.178). Mean SG utility values ranged from 0.46 to 0.85 among men with prostate cancer, 0.37 to 0.75 for men at risk, and 0.32 to 0.81 among the general population group.

Conclusions: There were no statistical differences between 16 disease-specific health states, but overall, the utility values calculated from the HUI were higher than utility values from the SG interview and utility values from patient were higher than the general population.

Introduction

There are numerous aspects of one's quality of life, including health specific components such as, physical functioning, emotional functioning and social functioning [1]. Health-related quality of life (HRQoL) can influence treatment options and decision-making for both the clinician and the patient. For use in a preference-based study, HRQoL attributes are written as a health state. A health state reflects presence, frequency, intensity of symptoms, abilities, and feelings and is valuated to measure an individual's well-being or satisfaction in that state [1]. The value assigned to a health state, preferred to as a preference weight or utility values, has application in health economics research, cost-effectiveness modeling, and evidence based medicine.

HRQoL plays an important role in prostate cancer given the long duration of life, occurrence of symptoms, and potential serious side effects from treatment. A review of utility values for prostate cancer outcomes found variations depending on the method when eliciting preferences, study population, various context effects, and mode of presentation [2]. This finding emphasizes the inability to compare results without understanding the context of the study, participants, and data collection methods. Similar studies have examined differences in preferences based on the perspective used for the valuation but the effect of perspective and method of elicitations has not been explored in prostate cancer [3].

Health states can be evaluated from the patient (post-illness) perspective, the societal perspective, or a different, unique, perspective. There is no consensus on the preferred perspective. Welfare economic theory supports the perspective of the health state affected person as the preferred source of utility valuation whereas extra-welfarist theory supports a generic and community-based preference to allow for comparison of preferences across disease categories and for use in allocating limited recourses [4]. The extra-welfarist believes that the post-illness preferences would too often result in the provision of marginally beneficial care and are subject to change and adaption [5]. Given the strengths, limitations, and biases of both the patient and societal preferences, understanding the difference and the consequence of selection on decision-making warrants further investigation.

To understand the difference in utility values by perspective, three different study populations were recruited: the patient perspective (men diagnosed with prostate cancer), the general population perspective, and men at risk for prostate cancer (elevated levels of prostate specific antigen). While those at risk for the disease is not a traditional perspective used in the application of cost-effective modeling, this population may anticipate or imagine the health state more clearly than the general population due to their clinical status. Any difference between utility values because of the perspective or the elicitation method can have a direct implication on results of a cost-effectiveness analysis.

The objective of this study was to compare utility values from the patient perspective, the societal perspective, and a population at-risk for prostate cancer using disease-specific health states and a generic preference measure. The results from this study will have application in cost-effectiveness research and provide the relationship between perspectives and between methods for prostate cancer outcomes.

Methods

The cross-sectional study recruited participants from three separate populations: men with prostate cancer, men at risk for prostate cancer, and a sample of the general population representative of the western Washington region. The eligibility criteria and sampling frame for each group is included in the Introduction Chapter. Disease-specific health states with prostate cancer outcomes were developed based on a review of the literature. The study population assigned value to the health states using a visual analog scale (VAS) and standard gamble (SG) methodology. Participants also completed the Health Utilities Index (HUI) to obtain utility values using a generic preference measure. At the completion of the study visits, participants completed a socio-demographic questionnaire to characterize the sample. An overview of the study visit and measures are included in the Introduction Chapter.

Disease-Specific Health States

The prostate cancer outcomes for the health states were developed based on a review of the literature [Described in detail in the Introduction Chapter]. The health states included five attributes, each with three levels of severity: sexual function, urinary function, bowel function, pain, and fear of the future. The health state description with attributes and levels, by valuation set, are presented in Table I-1. Each health state is assigned a 5-digit numeric code to signify the level of each attribute. The order of the attributes in the health state is represented by the place in the 5-digit code; there is one digit for each attribute, with the first digit representing the first attribute listed in the health state (sexual function) and the fifth digit representing the last attribute (fear of the future). The numeric value in the code represents the level of the attribute: level 1 is the least severe (no/none) and level 3 is the most severe state (always/considerable). Based on this coding scheme; health state 11111 is least severe health state and health state 33333 is the most severe health state.

Statistical Analysis

Descriptive statistics were reported for the socio-demographic data, HUI mark 2 (HUI2) and HUI mark 3 (HUI3) utility values, and the utility values for each disease-specific health state. Mean, standard deviation, median, and range reported for continuous variables and categorical variables were summarized in terms of frequency and percentages. To understand if perspective influences utility values, an analysis of covariance (ANCOVA) model and pair wise comparisons for each health state was conducted to compare between groups. All analyses were conducted in STATA/IC version 12.1.

Results

Study Sample

A total of 136 study participants completed the study visit (n=40 men with prostate cancer; n=43 men at risk for prostate cancer; n=49 general population). The pooled sample included 4 participants who were eligible at the time of screening and turned 71 years old before their scheduled interview visit. These participants were not included in the group comparisons, since they were not eligible for participation at the time of the study visit. The demographic characteristics of the study population are presented in Table 4. Overall the mean age was 55.5 years (SD 13.45), the majority were male (n=108; 79.4%), and Caucasian (n=108; 79.4%).

The sample of men at risk for prostate cancer were on average 60.2 years old (5.97), Caucasian (n=31; 77.5%), employed full or part time (n=20; 50.0%), had a college or post-graduate degree (n=22; 55.0%), and were married (n=24; 60.0%). A majority of the men reported that they live with someone (n=24; 60.0%) and less than half reported having children (n=14; 35.0%). Study participants were asked if they had a trusting relationship with their physician and if they consider themselves religious. These questions were included to address potential contributing factors to the valuation exercise. In the men at risk for prostate cancer population, the majority reported a trusting relationship with their physician (n=38; 95.0%) and just over half were religious (n=25; 62.5%).

The demographics of the men with prostate cancer were similar to those at risk for prostate cancer. The mean age was 63.4 years (5.46), the majority were Caucasian (n=39; 90.8%), had a college or post-graduate degree (n=27; 62.8%), and married (n=38; 88.4%) with approximately half retired (n=23; 53.5%). The majority reported living with someone (n=38; 88.4%) and having children (n=24; 79.1%). All of the men with prostate cancer reported a trusting relationship with their physician and just about half reported being religious (n=20; 46.5%).

The general population group was younger than the other groups with the mean age 43.2 years (14.09), with the majority Caucasian (n=34; 69.5%), working full or part time (n=35; 71.4%), and had a college or post-graduate degree (n=31; 63.3%). The general population group was more evenly divided in marital status with less than half single (n=24; 40.8%). The sample was fairly split in living condition and less than half reported having children (n=20; 40.8%). A majority of the sample reported having a trusting relationship with their physician (n=40; 81.6%) and just about half reported being religious (n=20; 40.8%).

Disease-Specific Health State Utility Values

In total, 816 health state valuations were elicited (6 health states for 136 participants). The mean values for each health state and the comparisons between groups are shown in Table III-2. Significant differences between perspectives were observed for two of the 18 health states (12231 and 22311). For these health states, the general population participants reported higher utility values compared the men at risk for prostate cancer (0 = least desirable state and 1 = most desirable state). While there was no statistically significant difference between the general population and men with prostate cancer, there was a trend for higher utility values in men with prostate cancer.

The general population group had the widest range of mean health state utility values and the lowest valuation for the worst health state (33331) (range 0.32 – 0.81). The men with prostate cancer valued the best health state (11212) with the highest utility value and rated the least desirable health state higher than the other two groups (range 0.46 – 0.85). The mean utility values for men at risk for prostate cancer ranged from 0.37 to 0.75. In general the men with prostate cancer rated health states higher (more desirable) compared to the general population and men at risk for prostate cancer, providing the highest value for 12 of the 18 health states. Men at risk for prostate cancer rated health states lower (least desirable) for 9 of the 18 health states and the general population rated health states lower for 8 of the 18 health states. While mean utility values for health states are heavily weighted towards the higher end of the scale, the participants used a large proportion of the 0 (death) to 1.0 (perfect health) continuum: with mean values ranging from 0.32 to 0.85 overall.

Generic Utility Values

Mean HUI2 and HUI3 values were comparable for the men with prostate cancer and the men at risk for prostate cancer and higher for the general population group (Table III-3; Figure I-1). While there was no statistically significant difference in mean values between groups, the mean value was lowest for men with prostate cancer (HUI3: 0.75, SD=0.26) and highest for the general population (HUI3: 0.84, SD=0.178). The mean values of the HUI2 and HUI3 for the general population group represents adults age 20 to 70 years old. The health states for this group may be heavily dependent upon age and reflected in the HUI values. The mean value for the HUI was stratified based on age: general population less than 45 years old and the general population greater or equal to 45 years (to match the age of the men at risk for prostate cancer and the men with prostate cancer). When stratified by age, there is a statistically significant difference in mean utility value for the HUI2 and the HUI3 for the general population group ($p<0.05$) [Table I-6]. The mean HUI2 and HUI3 for the general population sample ≥ 45 years old decreases compared to the HUI values for the total group, more closely matching the HUI mean value for the men at risk for prostate cancer and men with prostate cancer [Table I-4].

Figure I-2 series show the mean utility value calculated from the HUI2 and HUI3 and for each disease-specific health state for the general population group. The mean utility values calculated from the HUI is greater (closer to 1.0) compared to the utility values from the disease-specific health states. A similar observation is seen in the men with prostate cancer group and the men at risk for prostate cancer.

Discussion

This study was conducted to understand if different perspectives (men with prostate cancer, men at-risk for prostate cancer, and members of a general population) and different methods for utility elicitation (SG and HUI) influence utility values in the context of prostate cancer. Utility values, or more broadly, preference values have application in economic modeling to assess the incremental benefit relative to cost of new technologies. Preference values can be obtained from patients currently experiencing a certain health state, from people with past experience of that health state, close relatives of patients, health care professionals, and from samples of the general public [3]. Societal preferences are intended to measure comparable sources of data for disease-specific states and may be more valid in the context of decisions on the alternative allocation of resources [6]. The patient perspective may be more appropriate as they reflect the preferences of those most directly affected by an intervention or policy [7]. This study was designed to directly compare the preference values of 18 prostate cancer-specific health states between three different perspectives: the patient perspective, the societal perspective, and a population at risk for the disease and to measure preference values using the disease-specific health states and a generic preference measure (HUI). The use of three different populations and two different methods in the same study design for prostate cancer has not been previously published.

Overall, there was no statistically significant difference between groups in utility values for the 18 prostate cancer-specific health states, although there was a trend toward higher SG values from the men with prostate cancer as compared to the other groups. This trend is supported in the literature, where patients with the disease generally rate health states higher than the general population [3]. Overall, utility values for the 18 health states were high, with the data skewed towards 1.0 (most desirable state). Utility values for prostate cancer symptoms tends to be high with one study reporting the following mean utility values of prostate cancer treatment complications: sexual function = 0.89 (range: 0.74-1.0), urinary symptoms = 0.87 (range 0.71-1.0), and bowel dysfunction = 0.71 (range: 0.45 – 0.97) [20].

There was a smaller difference between groups for the HUI2 and HUI3 compared to the disease-specific utility values; with the smallest difference between the men with prostate cancer and men with elevated PSA levels. Smaller differences are expected between these two groups given the similar age, gender, and like disease states. While larger differences were observed between the general population group and men with prostate cancer and the general population group and men at risk for prostate cancer, there was still a smaller difference in mean HUI2 and HUI3 values compared to the mean utility values for the disease specific health states. The first version of the HUI was developed to evaluate outcomes for very-low birth weight infants and the most important attributes was determined for the HUI2 to address the global morbidity burden of childhood cancer reflecting both the form and severity of cancer sequelae [8]. The HUI was developed to address some concerns about the definitions of HUI2, to be applicable in both clinical and general population studies, and to have structural independence among the attributes; attributes are structurally independent of each other if all combinations of levels in the system are possible [8]. Across the HUI2 and HUI3 attributes of the same name have difference underlying constructs: HUI2 Emotion is concerned with distress and anxiety while HUI3 Emotion focuses on happiness versus depression, HUI2 Cognition concentrates on learning whereas HUI3 focuses on ability to solve day-to-day problems, HUI2 Pain includes frequency of pain and type of control and HUI3 Pain considers severity of pain [8].

These observations in difference of mean values inform the selection of using a disease-specific or generic preference measure to obtain utility values for prostate cancer outcomes, and highlight the importance of understanding the implications of the decision. A generic, preference based measure, such as the HUI does not include attributes specific to prostate cancer; such as, sexual functioning, urinary function, and bowel functioning contributing to less divide between men experiencing the attributes and a general population group without experience with the attributes. This is in contrast to the disease-specific health states, where a greater difference in mean values was observed. This would be expected since the attributes are directly applicable to the men with prostate cancer and imaginable by men with elevated PSA levels but not experienced by the general population group. While these differences are expected, one should be aware of the implications when selecting a generic preference based measure or disease specific health states in conditions where the disease specific attributes are not fully captured in the classification system for the generic measure.

The utility values from the general population included the perspective of men (n=21) and women (n=28) for the prostate cancer specific health states. An ad-hoc analysis was conducted to explore the difference in gender within the general population group [Table I-5]. The mean utility values for men in the general population group ranged from 0.27 to 0.91 compared to the mean utility values for females, which ranged from 0.36 to 0.77. The small sample sizes limit the ability to detect statistical differences. In this study, male respondents placed higher valuations on the more desirable health states and the females place higher valuations on the less desirable health states. There was a statistically significant difference between the men and women in one of the 18 health states (11212), the most desirable health state, with the men rating the state higher than the females ($p<0.05$). The influence of perspective for breast cancer specific health states was investigated comparing women with breast cancer, general practitioners, university staff, nurses, and hospital doctors [9]. In addition to finding that women with breast cancer rated health states higher (more desirable) compared to those with no direct experience with breast cancer, they found no statistically significant difference in utility values comparing female breast cancer patients with males.

Utility values derived from the HUI (generic preference measure) were higher than utility values derived from the SG (disease-specific health states) for prostate cancer. This is an important consideration when deciding upon a measure to use in obtaining utility values. The higher values (closer to perfect health) calculated from the HUI, from all three perspectives, indicates that the measure may not be sensitive enough to capture the disutility of prostate cancer symptoms; specifically, sexual dysfunction, urinary dysfunction, and bowel dysfunction that are being directly measured in the disease-specific health states.

There are several implications of the study design on the interpretation of the results. First, the definition of health states will impact the utility values. The results from this study can only be interpreted for the attributes in the health states, which we believe accurately, reflect concepts that are important to patients with prostate cancer. Second, valuation of health states is sensitive to the method of elicitation. Preference elicitation is possible through indirect and direct methods and each method produces different results with their own set of biases and limitations.

Strength of this study was the single interviewer completing all study participant interviewers, eliminating the potential for interviewer bias. Interviews were completed in-person, with the use of a standard gamble chance board to allow for the interviewer to assess the comprehension on the study participant to complete the task and review a sample scenario, several times if needed. The average time to complete the exercise was 17.9 minutes (SD: 5.61), with similar time for completion in each study group (men with elevated PSA: 17.6 min SD = 5.20; men with prostate cancer: 17.9 min SD = 6.73; general population: 18.1 min SD = 4.91). But it is equally important to note the limitations of the study. Generalizability of the study results is limited to the eligibly criteria of the study population. Study participants were recruited using the CSS database, clinic records at the UWMC, and the Department of Licensing database, all in the western Washington region. The demographic characteristics of the general population sample were compared to the demographic characteristics of participants enrolled in the Medical Expenditure Panel Survey Household Component (MEPS data; 2013). A greater proportion of participants in the study were employed (71.4% vs 46.7% in MEPS), with similar distribution of gender (42.8% vs 48.8% in MEPS), similar distribution of race (Caucasian: 69.5% vs 62.4% in MEPS), and similar distribution of marital status (Married: 32.7% vs 39.7% in MEPS). In addition the small sample may have limited the ability to detect difference between groups. The sample size was based on the one-sided hypothesis that the general population utility values will be lower than the patient preference values. A sample size to detect this difference is approximately 40-50 participants in each group. To reduce the burden on the study participants, the 18 health states were grouped into three sets, reducing the total sample valuing each health state.

Areas for further research include the use of statistical modeling to predict health state valuations for the disease-specific health states from the five attributes and three levels. The statistical model will address the weight of the specific attributes and determine which covariates may contribute to the valuations of the health states. While SG has been considered the preferred method for utility measurement, there is empirical evidence demonstrating that expected utility is not descriptively valid and that its violations generate upward biases in SG utilities [10]. To further explore the difference between perspectives, it is recommend using the disease-specific utility values in a cost-utility model to determine if and to what degree the experience of a health state affects the incremental cost-effectiveness ratio.

Table I-1. Health State Descriptions

Health State Card	Experience problems with achieving and maintaining an erection	Experience problems with urination	Experience problems with diarrhea and / or constipation	Experience pain that limits your activities	Experience fear of the future
A.1	1	3	1	2	1
A.2	2	1	2	2	1
A.3	3	2	1	3	2
A.4	1	3	3	1	3
A.5	2	1	3	3	2
A.6	3	2	2	1	3
B.1	2	3	1	1	2
B.2	1	2	2	3	1
B.3	1	1	1	3	3
B.4	3	1	3	2	3
B.5	2	2	3	1	1
B.6	3	3	2	2	2
C.1	2	3	2	3	3
C.2	2	2	1	2	3
C.3	1	2	3	2	2
C.4	1	1	2	1	2
C.5	3	1	1	1	1
C.6	3	3	3	3	1

Level 1: never; Level 2: sometimes; level 3: always

Table I-2. Mean Standard Gamble Preference Values by Study Group

	Men at Risk for Prostate Cancer N, Mean (SD)	Men with Prostate Cancer N, Mean (SD)	General Population N, Mean (SD)	Overall F value	Pairwise Comparisons
12231	13, 0.51 (0.259)	15, 0.61 (0.313)	16, 0.75 (0.173)	3.49	2*
22311	13, 0.65 (0.231)	15, 0.75 (0.136)	16, 0.79 (0.112)	3.06	2**
11212	12, 0.72 (0.192)	14, 0.85 (0.145)	16, 0.81 (0.182)	1.95	NS
33222	13, 0.56 (0.237)	15, 0.70 (0.200)	16, 0.68 (0.195)	1.86	NS
32132	15, 0.61 (0.253)	15, 0.65 (0.218)	17, 0.50 (0.239)	1.79	NS
31111	12, 0.67 (0.148)	14, 0.79 (0.164)	16, 0.74 (0.215)	1.57	NS
23233	12, 0.50 (0.227)	14, 0.58 (0.276)	16, 0.43 (0.214)	1.54	NS
12322	12, 0.56 (0.182)	14, 0.69 (0.206)	16, 0.63 (0.191)	1.48	NS
21332	15, 0.62 (0.246)	15, 0.66 (0.196)	17, 0.54 (0.193)	1.25	NS
33331	12, 0.37 (0.228)	14, 0.46 (0.309)	16, 0.32 (0.197)	1.14	NS
13121	15, 0.75 (0.196)	15, 0.78 (0.135)	17, 0.67 (0.267)	1.13	NS
22123	12, 0.54 (0.212)	14, 0.65 (0.255)	16, 0.55 (0.191)	1.08	NS
21221	15, 0.74 (0.198)	15, 0.80 (0.161)	17, 0.69 (0.262)	1.03	NS
31323	13, 0.58 (0.258)	15, 0.70 (0.206)	16, 0.65 (0.182)	1.02	NS
23112	13, 0.71 (0.249)	15, 0.77 (0.167)	16, 0.80 (0.122)	0.90	NS
11133	13, 0.53 (0.274)	15, 0.60 (0.326)	16, 0.63 (0.208)	0.49	NS
13313	15, 0.67 (0.243)	15, 0.62 (0.192)	17, 0.67 (0.213)	0.21	NS
32213	15, 0.69 (0.177)	15, 0.68 (0.160)	17, 0.65 (0.249)	0.19	NS
Range of mean values	0.37 – 0.75	0.46 – 0.85	0.32 – 0.81		

Analysis of covariance (ANCOVA) model; Pairwise comparisons tested by Bonferroni
Comparisons: 1 = Group 1 vs. 2; 2 = Group 1 vs. 3; 3 = Group 2 vs. 3
* $p<0.05$; ** $p=0.05$
SG valuations range from 0 (death) to 1.0 (perfect health)
Order of health states: Sexual functioning, Urinary functioning, bowel functioning, pain, emotional well-being: 1 = least severe 3 = most severe

Table I-3. Health Utilities Index Mark 2 and Mark 3 Utility Scores

	Pooled Sample* (n=136)	Men at Risk for Prostate Cancer (n=40)	Men with Prostate Cancer (n=43)	General Population (n=49)
HUI mark 2				
Mean (SD)	0.84 (0.143)	0.83 (0.168)	0.83 (0.124)	0.87 (0.136)
Median [range]	0.89 [0.295, 1.0]	0.89 [0.295, 1.0]	0.85 [0.460, 1.0]	0.90 [0.311, 1.0]
HUI mark 3				
Mean (SD)	0.79 (0.228)	0.77 (0.238)	0.75 (0.260)	0.84 (0.178)
Median [range]	0.86 [-0.039, 1.0]	0.85 [-0.030, 1.0]	0.84 [-0.040, 1.0]	0.91 [0.282, 1.0]

* Pooled sample includes 4 participants with age >70 years at the time of screening

Table I-4. Health Utilities Index Mark 2 and Mark 3 Utility Scores Stratified by Age

	HUI2 Mean (SD)		HUI3 Mean (SD)	
	Age < 45	Age ≥ 45	Age < 45	Age ≥ 45
Men at Risk for Prostate Cancer		0.83 (0.168)		0.77 (0.238)
Men with Prostate Cancer		0.83 (0.124)		0.75 (0.260)
General Population	0.91 (0.016)	0.80 (0.040)	0.90 (0.021)	0.76 (0.052)

Table I-5. Descriptive Statistics of Standard Gamble Preference Values by Gender

Health State	Men with Prostate Cancer (n=43) N, mean (SD)	General Population Men (n=21) N, mean (SD)	General Population Women (n=28) N, mean (SD)
11212	14, 0.85 (0.145)	7, 0.91 (0.043)	9, 0.73 (0.064)
21221	14, 0.79 (0.161)	7, 0.70 (0.078)	10, 0.68 (0.097)
31111	14, 0.79 (0.164)	7, 0.73 (0.105)	9, 0.76 (0.057)
23112	15, 0.77 (0.167)	7, 0.84 (0.051)	9, 0.77 (0.036)
13121	14, 0.77 (0.131)	7, 0.69 (0.086)	10, 0.66 (0.096)
22311	15, 0.75 (0.136)	7, 0.83 (0.026)	9, 0.77 (0.045)
31323	15, 0.70 (0.206)	7, 0.60 (0.097)	9, 0.69 (0.032)
33222	15, 0.70 (0.200)	7, 0.66 (0.110)	9, 0.69 (0.027)
12322	14, 0.69 (0.206)	7, 0.65 (0.092)	9, 0.61 (0.050)
32213	14, 0.66 (0.147)	7, 0.59 (0.117)	10, 0.70 (0.063)
22123	14, 0.65 (0.255)	7, 0.59 (0.068)	9, 0.52 (0.068)
21332	14, 0.64 (0.186)	7, 0.59 (0.052)	10, 0.52 (0.072)
32132	14, 0.64 (0.219)	7, 0.44 (0.082)	10, 0.54 (0.081)
12231	15, 0.61 (0.310)	7, 0.81 (0.062)	9, 0.71 (0.057)
13313	14, 0.60 (0.175)	7, 0.55 (0.093)	10, 0.75 (0.047)
11133	15, 0.60 (0.326)	7, 0.61 (0.109)	9, 0.66 (0.043)
23233	14, 0.58 (0.276)	7, 0.39 (0.079)	9, 0.45 (0.076)
33331	14, 0.46 (0.309)	7, 0.27 (0.080)	9, 0.36 (0.063)
Range of mean values	0.46 – 0.85	0.27 – 0.91	0.36 - 0.77

SG valuations range from 0 (death) to 1.0 (perfect health)
Order of health states: Sexual functioning, Urinary functioning, bowel functioning, pain, emotional well-being: 1 = least severe 3 = most severe

Figure I-1. Health Utilities Index Mark 2 and Mark 3 Utility Scores

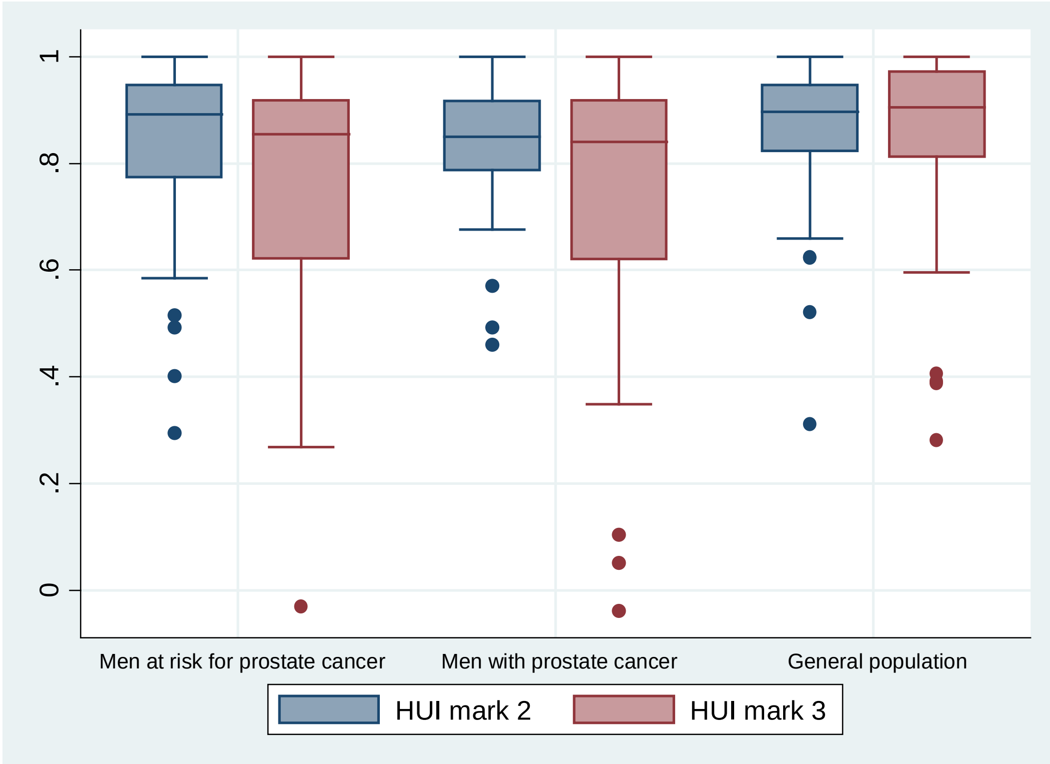


Figure I-2a. Utility Values for the General Population Comparing Disease-Specific Generic Elicitation Methods

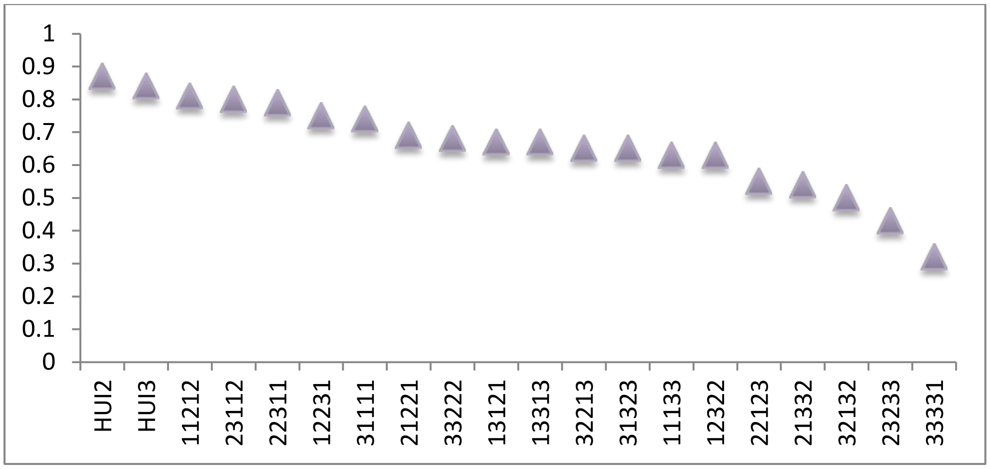


Figure I-2b. Utility Values for Men with Prostate Cancer Comparing Disease-Specific Generic Elicitation Methods

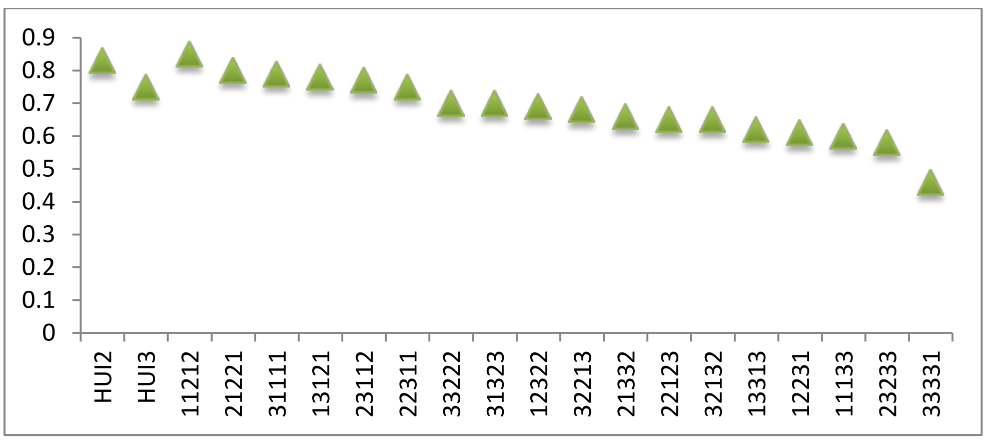
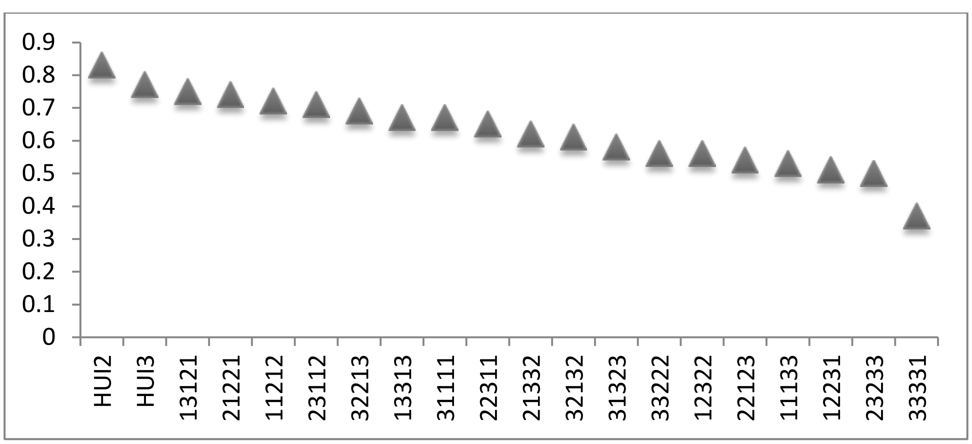


Figure I-2c. Utility Values for Men at Risk for Prostate Cancer Comparing Disease-Specific Generic Elicitation Methods



Chapter II: Estimating Prostate Cancer Utility Values from Disease Specific Health States

Abstract

Objective: To develop a statistical model that generates utility values for prostate cancer specific health states, using preference weights derived from three different perspectives.

Methods: Utility values were calculated from men at risk for prostate cancer, men with prostate cancer, and the general population using standard gamble (SG) methodology. Study participants valued 18 prostate-specific health states with the following attributes: sexual function, urinary function, bowel function, pain, and emotional well-being. A linear regression model accounting for clustering, mixed effects model, and generalized estimating equation were tested to determine which was most appropriate to generate prostate cancer utility values. Appropriateness of model was determined based on correlations between the observed and predicted health state values.

Results: 132 study participants assigned value to the health states (n=40 men at risk for prostate cancer; n=43 men with prostate cancer; n=49 general population). In total, 792 health state valuations were elicited (6 health states for each 132 participants). The most appropriate model was a mixed effects model. When correcting for loss aversion the corrected mean SG values were smaller than the observed utility values (obs mean: 0.64, SD: 0.24; corr mean: 0.47, SD: 0.25).

Conclusions: Developing a health state classification system with preference weights for three different perspectives demonstrates the relative importance of main effects between populations. The predicted values for men with prostate cancer support the hypothesis that patients experiencing the disease state assign higher utility values to health states and there is a difference in valuations made by patients and the general population.

Introduction

Preference weights, or utility values, are necessary components of cost-utility analyses (CUA) and calculating quality adjusted life year (QALY) estimates. The cost-utility model generates an incremental cost-effectiveness ratio (ICER) to quantify the additional cost per extra unit of effect (QALY) comparing two or more interventions. The QALY represents the duration of an individual's life accounting for changes in health over time.

CUA originates in constrained optimization; it is used as an index of benefit that can inform resource allocation decisions across a range of disease areas and therapeutic interventions [1]. The United Kingdom National Institute for Health and Care Excellence (NICE) issued a guidance stating preference for economic evaluations using generic preference-based utility measures, specifically the EuroQol EQ-5D [2]. The guidance states that in the absence of EQ-5D data, empirical mapping of the EQ-5D from other health related quality of life (HRQoL) instruments or the valuation of health states from other HRQoL instruments may be used as an alternative [2]. Another method for obtaining preference-based utility values includes the use of direct elicitation based on expected utility theory [3]. The four axioms of expected utility theory are: completeness, transitivity, continuity, and independence. If all four axioms are accepted then it follows that outcomes can be assigned numerical utility values, any choice can be assigned an expected utility, and choosing the option that maximizes one's expected utility is expected to give the most satisfaction [3]. The standard gamble (SG), a direct elicitation method, satisfies the four axioms of expected utility theory.

Utility values informing the QALY index are measured on an interval scale between 0 and 1, where the scale anchors represent death (value of 0) and full health (value of 1.0), respectively [4]. The SG, time trade-off (TTO), or rating scale (RS) can be used to directly value utility informing the QALY or utility values can be obtained indirectly using “off the shelf” preference-based measures such as the EQ-5D or the Health Utilities Index (HUI) [4]. Mean utility values vary according to perspective (patients or members of the general population) and elicitation method (SG, TTO, or RS). Most studies have shown that patients rate their own health states higher than the general population rating the same states; the difference may arise because patients have adapted to their condition or because the general population overestimates the impact of disability or disease on quality of life [5, 6]. Utilities for outcomes in prostate cancer are of unique importance, but generic measures do not represent prostate cancer outcomes such as sexual, urinary, and bowel dysfunction well and may not capture their full impact [7].

A review of utility values for prostate cancer outcomes found that values for bowel problems were lower than those for sexual or urinary problems and utilities for multi-attribute health ranged from 0.05 for metastatic cancer with severe pain, fatigue, hot flashes, loss of libido, and impotence to 1.0 for non-metastatic cancer with minimal symptoms [5]. The Patient-Oriented Prostate Utility Scale (PORPUS) health state classification system includes 10 domains: pain and disturbing body sensations, energy, support from family and friends, communication with doctor, urinary frequency, leaking urine/poor bladder control, sexual function, sexual drive and interest, and bowel problems [7]. The valuation of the classification system was from the patient perspective and the disease-specific preferences were compared to community preferences from the Health Utilities Index (HUI) and the Quality of Well Being Scale (QWB) [8]. The valuation of the PORPUS health states and development of the classification system were not assessed from the community or societal perspective. The comparison of preference values from the patient perspective using disease-specific health states and preference values from the community using a generic measure is important but does not address the difference in valuations when patients and community members without the disease are assigning disease-specific preference weights with the same classification system.

To address the comparison between patient and societal perspectives using the same classification system, prostate cancer health states were developed based on a review of the literature which identified five outcomes relevant to patients' experience with prostate cancer (sexual functioning, urinary functioning, bowel functioning, pain, and fear of the future) [Described in detail in the Introduction Chapter]. The five attributes created 243 possible multi-attribute health states that were valued by three different perspectives to understand if the valuations, or preference weights, differ based on perspective of respondent. The objective of this study was to use the preference weights of 18 health states to generate a model that can be used to predict preference weights for all 243 health states for population-based preference weights, patient-based preference weights and a third unique perspective, men at risk for prostate cancer. This article provides an overview of the elicitation of the utility values for the three different perspectives and focuses on the algorithm to determine the preference weights for the prostate cancer classification system.

Methods

The valuation sample included data collection from the three study groups: men at risk for prostate cancer, men with prostate cancer, and participants from the general population in the western Washington region (King, Kitsap, Pierce, and Snohomish counties) in the United States. Eligibility criteria and the sampling frame for each group is described in detail in the Introduction Chapter.

The descriptive system includes 243 health states, and valuations were obtained for 18 of the health states selected using an orthogonal experimental design and grouped into three sets.

Each participant was randomly assigned to one of the three groups and valued a total of 6 health states (Table II-1). In addition to collecting the disease-specific utility values, data were collected on age, gender, living situation, marital status, employment, education level, racial/ethnic background, and concomitant medical conditions for the study participants. Participants were also asked if they considered themselves to be religious and if they have a trusting relationship with their physician. Demographic characteristics such as age, education, gender, religion, race, and marital status were important covariates to collect given their potential influence on preference valuations [9-14].

Statistical Analysis

The aim of the analysis was to determine an appropriate model to predict heath state valuations for the 243 prostate cancer specific health states and to generate parameter estimates for the three different populations: at risk for the disease state, patient perspective, and the general population.

Model Development

A number of different models were investigated to determine the appropriate fit for estimating SG values. Multi-level regression models were tested given the clustering of health states values within study participants. *A-priori* models included a linear regression model, a mixed effects model and generalized estimating equations (GEE) with various distributions and link functions [15-17]. To account for heteroscedasticity in the sample, Huber-White standard errors were applied [18]. Comparison of models to determine the best fit was assessed based on inconsistencies in regression coefficients, the number of significant coefficients, and comparison of observed and predicted values. As the severity of the level increases, it is expected that there would be greater disutility of the attribute. An inconsistency in the regression coefficient would be less disutility with greater severity of the attribute. Paired t-tests were used to compare observed and predicted values.

Variables

The dependent variable was the SG utility value; a continuous variable ranging from 0 (death) to 1.0 (perfect health). Independent variables included the main effects from the health state classification system. The least severe level in each health state attribute was coded as the reference dummy variable so two dummy variables were included for each health state in the regression model: sexual function (S2, S3), urinary function (U2, U3), bowel function (B2, B3), pain (P2, P3), and fear of the future (F2, F3). Age, education, gender, religion, race, and marital status were included as covariates in the model.

Bias Correction

While SG has been considered a preferred method for utility measurement, there is empirical evidence demonstrating that expected utility is not descriptively valid and that its violations generate upward biases in SG utilities [13]. Loss aversion refers to the finding that people are more sensitive to losses than to gains; consequently, losses weight more heavily in decisions than gains [13]. Mixed-corrected standard SG utility values to account for loss aversion were calculated based on prospect theory [13]. In the SG exercise, for a person who is averse to loss, the gain probability P must then be extra high to offset the loss probability (1-P) and loss aversion therefore generates as upward bias in SG utility values [13]. To correct for the bias of loss aversion, Tversky and Kahneman propose a weighted probability function for losses and gains (0.69 for losses and 0.61 for gains) [19].

Results

A total of 132 participants completed the study visit and SG valuation exercise (n=40 men at risk for prostate cancer; n=43 men with prostate cancer; n=49 men and women from the general population). Men with prostate cancer were statistically different from the general population in terms of age, gender, employment status, and relationship status testing for group comparison of means. The distribution of SG health state valuations is provided in Figure II-1. In total, 792 health state valuations were elicited (6 health states for each 132 participants). The mean SG value was 0.64 (SD: 0.235), median value was 0.65 (range 0 – 1.0).

<u>Valuation Model</u>

The appropriate modeling strategy was not clear a-priori, without first understanding the distribution of the valuation data. The SG health state values were skewed towards 1.0, influencing the choice of model. In addition, the health state values were likely to be clustered by participant. Individuals did not value the same set of states, although allocation of states to individuals was random, the differences between health state values may be due to differences in preferences of the individuals, rather than the attributes of those states [15].

Table II-2 provides the parameter estimates of four different models for the estimation of SG utility values. Model 1 was a least squares linear regression, accounting for within-individual clustering, and assuming a standard zero mean, constant variance error structure, and independent error terms. Model 2 was a mixed effects model accounting for both within and between individual error components. Models 3 and 4 were GEE models with a gamma distribution in two different functional forms (log link and power link). The GEE model estimates within-cluster similarity of the residuals and uses the estimated correlation to re-estimate the regression parameters and to calculate standard errors [16-17]. While age and gender were not found to be statistically significantly different from no effect on SG values, they were retained because prostate cancer is age and gender dependent. Education, marital status, and race were retained based on the statistical significance of the parameter estimates.

The most appropriate model was the mixed effects model because of the stronger correlations between the observed and predicted health state valuations. The observed and predicted health state values, by study population, for the 18 health states included in the SG valuation exercise are included in Table II-3. There were no statistically significant differences between the observed and predicted values in the men at risk for prostate cancer group and the men with prostate group. For the general population group there were three health states (*22311; 12231; 33331*) with a predicted value significantly different than the observed value (Table II-3). Higher valuations (closer to most desirable health state) were observed for men with prostate cancer compared to men at risk for prostate cancer and the general population group (both with similar ranges).

Model fit was also determined by inconsistencies in regression coefficients and the number of significant coefficients. The main effects (sexual functioning levels, urinary functioning levels, bowel functioning levels, pain level, and fear of the future levels) were expected to be negative and increasing in absolute size from level 2 to level 3. An inconsistent result occurs where a coefficient on the main effects decrease in absolute size for a worse level (level 3 coded as the worst level) [15]. In all four models there were inconsistencies in the *Fear of the Future* attribute with level two having a positive coefficient. A positive coefficient was observed in the *Bowel Function* attribute in the GEE model with a power link function. The number of significant coefficients for the main effects was similar between the mixed effects model and the two different GEE models (7 significant coefficients).

The final model parameter estimates, for the fitted mixed effects model, for the total sample and each perspective are included in Table II-4. The gender variable is omitted in both the men at risk for prostate cancer and the men with prostate cancer groups given that only men are included in these samples. The final model allows for estimating all 243 possible health state combinations.

Comparing the main effects, the *sexual function* attribute level 2 was statistically significant for the general population group but not for the men at risk for prostate cancer or men with prostate cancer indicating that older men faced with prostate cancer place less emphasis on sexual functioning compared to the general population. Moderate *bowel function* was not statistically significant for all groups, indicating no difference between *no* bowel dysfunction and moderate bowel dysfunction in valuing health states. A similar observation was seen with *urinary function* level 2 for the general population group; but men at risk for or with prostate cancer differentiated between *no* urinary dysfunction and moderate urinary dysfunction. There was no statistical significance in the difference between *no* pain and moderate pain for men with prostate cancer, but significance was observed in the general population and men at-risk for prostate cancer. While there was significant difference observed for *fear of the future* level 3 (considerable fear) in both the men with prostate cancer and the general population, this was not observed in the men at risk for prostate cancer group. This finding is contradictory to the hypothesis that men at risk for prostate cancer may experience fear of a potential prostate cancer diagnosis and their unknown state of health.

Bias Correction

Figure II-2 shows the difference in the mean SG values (and range) from the SG valuation exercise and the corrected SG values (and range) for loss aversion. There was a statistically significant difference between the observed and corrected SG values for the study populations (men with prostate cancer: observed mean: 0.61, SD: 0.238, corrected mean: 0.44, SD: 0.243; men with prostate cancer: observed mean: 0.68, SD: 0.228, corrected mean: 0.51, SD: 0.248; general population: observed mean: 0.64, SD: 0.245, corrected mean: 0.46, SD: 0.243) and the total sample: observed mean: 0.64, SD: 0.235, corrected mean: 0.47, SD: 0.246). Correcting for biases shifts the utility value away from the participant making rational decisions based on the axioms of utility theory and accounts for deviation from rational decision making.

Discussion

Preference weights for 18 health states were used to generate a model that can be used to predict the preference weights for all 243 possible health states in a prostate specific health state classification system. The importance of developing a classification system for each perspective is based on the foundation that the patients adapt to their disease state causing an inflation of values, but members of the public may not be able to fully understand the experience of living with a disease or be able to imagine how their life might change in its presence [20]. Use of the different perspectives created different classification systems for the possible health states.

Interpretation of the results is dependent upon the selection of the final model and the assumptions within the statistical boundaries of the selected methods. The two most common statistical models for examining an association between a predictor of interest and a continuous outcome variable in data with clustering are GEE and mixed-effects linear regression models [21]. GEE models the marginal distribution of repeated observed outcomes as a function of risk factors while accounting for the dependence of the repeated outcome variable by assuming a certain working correlation structure. The mixed effects linear regression model allows either the intercept, or the regression coefficients, or both to vary between subjects. Standard goodness of fit statistics, such as R^2, AIC and BIC, cannot be done on GEE models limiting the ability to compare between models when determining the most appropriate. Given the similarities between the mixed effects model and GEE, the final model was selected based on the scientific question and the strength of correlations between observed valuations and predicted valuations.

The mixed-effects linear regression model allows for an assessment of the between subject and within subject effects, but the estimates may be biased if the distribution is miss-specified [20]. Additional investigation into the appropriate data transformation could be warranted but was not pursued given the authors' interest in maintaining the integrity of the distribution of the data and interpretation of utility values on a zero to 1.0 scale [20]. The constant coefficient in Model 4 (GEE with power link) was greater than 1.0 (c=1.0840). The constant coefficient is the outcome value (utility value) when all of the independent variables are set to 1.0. If all of the health state attributes were set to 1.0 then we would be modeling health state 11111, which is anchored at perfect health and a utility value greater than 1.0 is not possible. This model includes the following covariates: age, gender, race, education, and marital status, which complicates the interpretation of the constant term as all of those parameters would need to be set to the reference value. When using this model to calculate utility values, a scaling term needs to be included so that a utility value greater than 1.0 is not a possible outcome.

Available evidence suggests that experience of illness may influence respondent's valuations of health states; patients with a particular condition often assign a higher utility than do patients without the condition [22]. There was a clear difference in the valuations of the *sexual function* attribute when comparing the general population group with men at risk for prostate cancer and men with prostate cancer. The difference between levels was only significant for the general population group, which may be attributable to the difference in age between the groups. The general population group included men and women 18-70 years old, where the other two groups were inclusive of men 45-70 years old. Another hypothesized reason for this observation may be the inclusion of women in the general population group placing value on a health state describing men's sexual functioning.

Another notable difference between study groups was the lack of significance comparing moderate *pain* with no *pain* in the men with prostate cancer population. Men with prostate cancer are often familiar with pain as it is a common side effect of the cancer and its treatment. Therefore, they may down play the impact of moderate pain that limits their usual activities because of adaptation or acceptance of the symptom / disease state. The general population and men at risk for prostate cancer could possibly imagine that pain may cause a greater impact on their ability to function and health related quality of life. The third notable finding when comparing main effects between groups was the lack of statistical significance for *fear of the future* level 3 in men at risk for prostate cancer. This contradicts our hypothesis that being faced with the risk of disease would have a profound impact on emotional well-being. Of course, this may be a phenomenon of sample size and a larger sample and the valuation of additional health states may have overcome these discrepancies.

Cancer patients rated their current health state lower than volunteers for colorectal cancer screening [23]; supporting the finding in men at risk for prostate cancer rating emotional well-being higher than patients with cancer. The inconsistencies in the coefficient (positive value when it should be negative) observed in *sexual function* level 2, *bowel function* level 2, and *fear of the future* level 2 would need to be reexamined with a larger sample size to understand if the observation is model dependent and could be further explored in samples with similar ages.

An interesting finding when comparing the predicted health state valuations to the observed valuations for each study population was the similarities between the predicted values for men at risk for prostate cancer and the general population. Not only are several of the individual health states predicted to have the same value but the range is the same (0.44 for the lowest health state: 33331 and 0.82 for greatest health state: 11212). These results imply that a member of the general population may value prostate cancer specific health states similarly to men at risk for developing prostate cancer. The predicted values for men with prostate cancer support the hypothesis that patients experiencing the disease state assign higher utility values to health states and valuations made by patients differ from valuations made by the general population.

The results of the bias correction show the direction of change in utility value when moving away from rational decision making. The decrease in utility value, closer to 0 and the least desirable health state, implies that the health condition or disease state may have greater impact to one's health related quality of life than we observe. This puts more focus on interventions that may improve a patients' health related quality of life.

The study results should be interpreted within the context of limitations. First, the strength of the statistical model and significance of parameters would be enhanced by an increase in the sample size for each group. Because of the number of health states in the classification system, study participants did not value all 18 health states, but a random sample of 6 health states. Ideally and to improve the sample size, the participants would value all 18 health states to prevent the sample from being divided into thirds. Second, model fitting to a data set is a combination of decision making based on model fitting statistics and decision making based on the research question. Non-significant covariates were retained in the model based on the importance of the parameters for prostate cancer, but one may decide to remove those covariates based on statistical considerations, in which case the final model coefficients may change. Third, the study results are generalizable to the Western Washington region. Recruitment was designed to obtain a random sample of men with prostate cancer and a random sample of the general population, within the constraints of the sampling frame, but valuations made from those in the Western Washington could not be extrapolated to a national sample, without first comparing the demographics of the sample.

Table II-1. Health State Assignments for Valuation

Group A	Group B	Group C
13121	23112	23233
21221	12231	22123
32132	11133	12322
13313	31323	11212
21332	22311	31111
32213	22311	33331

Order of health states: Sexual function, Urinary function, bowel function, pain, emotional well-being: 1 = least severe 3 = most severe.

Table II-2. Parameter Estimates for Model Specifications

Variable	Model 1[1] (Linear regression) Coef. (SE)	Model 2 (Mixed effects model) Coef. (SE)	Model 3[2] (GEE: log link) Coef. (SE)	Model 4[2] (GEE: power link) Coef. (SE)
S2	-0.018 (0.0187)	-0.018 (0.0135)	-0.040 (0.0270)	-0.053 (0.0287)
S3	-0.061 (0.0187)*	-0.061 (0.0135)*	-0.115 (0.0234)*	-0.089 (0.0183)*
U2	-0.048 (0.0187)*	-0.048 (0.0135)*	-0.072 (0.0220)*	-0.058 (0.0197)*
U3	-0.073 (0.0187)*	-0.073 (0.0135)*	-0.138 (0.0314)*	-0.110 (0.0254)*
B2	-0.001 (0.0187)	-0.001 (0.0135)	-0.005 (0.0186)	0.009 (0.0160)
B3	-0.057 (0.0187)*	-0.057 (0.0135)*	-0.101 (0.0222)*	-0.069 (0.0187)*
P2	-0.063 (0.0187)*	-0.06 (0.0135)*	-0.093 (0.0235)*	-0.069 (0.0192)*
P3	-0.177 (0.0187)*	-0.177 (0.0135)*	-0.293 (0.0365)*	-0.186 (0.0241)*
F2	0.011 (0.0187)	0.011 (0.0135)	0.035 (0.0214)	0.031 (0.0159)*
F3	-0.053 (0.0187)	-0.053 (0.0125)*	-0.068 (0.0246)*	-0.041 (0.0263)*
Age	-0.001 (0.0006)*	-0.001 (0.0011)	-0.001 (0.0019)	0.001 (0.0007)
Gender				
Female	0.003 (0.0206)	0.0023 (0.0371)	0.018 (0.0618)	-0.026 (0.0238)
Race				
Non-white	-0.090 (0.0191)*	-0.090 (0.0345)*	-0.162 (0.0656)	-0.253 (0.0486)*
Education				
Some college	0.020 (0.0266)	0.020 (0.0479)	0.019 (0.0479)	-0.162 (0.0474)*
College degree	-0.027 (0.0256)	-0.027 (0.0461)	-0.047 (0	-0.197 (0.0394)*
Post-graduate	0.013 (0.0271)	0.013 (0.0488)	0.018 (0.0674)	0.020 (0.0824)
Marital Status				
Not married	-0.038 (0.0163)*	-0.038 (0.0294)	-0.063 (0.0521)	-0.177 (0.0664)*
Constant	0.873 (0.0497)*	0.873 (0.0800)*	-0.086 (0.1399)	1.084 (0.0693)*
Random-effects				
Constant		0.1445 (0.0106)		
Residual		0.1554 (0.0043)		
Model Fit Statistics				
$\mathbf{R^2}$	0.1846			
Root MSE	0.2146			

S = Sexual function; U = Urinary function; B = Bowel function; P = Pain; F = Fear of the future.
* P<0.05. Huber-White standard errors to adjust for heteroscedasticity.
[1] Linear model with standard errors adjusted for 132 clusters in participant ID. [2] Gamma distribution with exchangeable correlation matrix. [3] Binomial distribution with exchangeable correlation matrix.

Table II-3. Observed and Predicted Health State Valuations

Health State	Men at Risk for Prostate Cancer (n=40) Mean (SD)		Men with Prostate Cancer (n=43) Mean (SD)		General Population (n=49) Mean (SD)	
	Observed	**Predicted**	**Observed**	**Predicted**	**Observed**	**Predicted**
13121	0.75 (0.196)	0.69 (0.047)	0.77 (0.131)	0.71 (0.028)	0.67 (0.267)	0.69 (0.046)
21221	0.74 (0.198)	0.74 (0.047)	0.79 (0.161)	0.76 (0.028)	0.69 (0.262)	0.74 (0.046)
11212	0.72 (0.192)	0.82 (0.054)	0.85 (0.145)	0.84 (0.046)	0.81 (0.182)	0.82 (0.056)
23112	0.71 (0.249)	0.75 (0.039)	0.77 (0.167)	0.77 (0.020)	0.80 (0.122)	0.73 (0.046)
32213	0.69 (0.177)	0.66 (0.047)	0.66 (0.146)	0.68 (0.028)	0.65 (0.249)	0.66 (0.046)
13313	0.67 (0.243)	0.64 (0.047)	0.60 (0.175)	0.66 (0.028)	0.67 (0.213)	0.64 (0.046)
31111	0.67 (0.148)	0.75 (0.054)	0.79 (0.164)	0.77 (0.046)	0.74 (0.215)	0.75 (0.056)
22311	0.65 (0.231)	0.71 (0.039)	0.75 (0.136)	0.72 (0.020)	0.79 (0.112)	0.69 (0.046)*
21332	0.62 (0.246)	0.58 (0.047)	0.64 (0.186)	0.60 (0.028)	0.54 (0.193)	0.58 (0.046)
32132	0.61 (0.253)	0.55 (0.047)	0.64 (0.219)	0.57 (0.028)	0.50 (0.239)	0.55 (0.046)
31323	0.58 (0.258)	0.60 (0.039)	0.70 (0.206)	0.61 (0.020)	0.65 (0.182)	0.58 (0.046)
12322	0.56 (0.182)	0.65 (0.054)	0.69 (0.206)	0.67 (0.046)	0.63 (0.191)	0.65 (0.056)
33222	0.56 (0.237)	0.64 (0.039)	0.70 (0.200)	0.66 (0.020)	0.68 (0.195)	0.62 (0.046)
22123	0.54 (0.212)	0.63 (0.054)	0.65 (0.255)	0.65 (0.046)	0.55 (0.191)	0.63 (0.056)
11133	0.53 (0.274)	0.60 (0.039)	0.60 (0.326)	0.62 (0.020)	0.63 (0.208)	0.58 (0.046)
12231	0.51 (0.259)	0.61 (0.039)	0.61 (0.310)	0.62 (0.020)	0.75 (0.173)	0.58 (0.046)*
23233	0.50 (0.227)	0.49 (0.054)	0.58 (0.276)	0.51 (0.046)	0.43 (0.214)	0.49 (0.056)
33331	0.37 (0.228)	0.44 (0.054)	0.46 (0.309)	0.46 (0.046)	0.32 (0.197)	0.44 (0.056)*
Range	0.37 – 0.75	0.44 – 0.82	0.46 – 0.85	0.46 – 0.84	0.32 - 0.81	0.44 – 0.82

SG valuations range from 0 (death) to 1.0 (perfect health). Order of health states: Sexual function, Urinary function, bowel function, pain, emotional well-being: 1 = least severe 3 = most severe.
*Two group mean comparison test (comparing mean observed SG values and predicted mean SG values): $p<0.05$

Table II-4. Final Model Parameter Estimates for Population Groups

Variable	Total Sample (n=792) Coef. (SE)	Men at Risk for Prostate Cancer (n=240) Coef. (SE)	Men with Prostate Cancer (n=258) Coef. (SE)	General Population (n=294) Coef. (SE)
S2	-0.018 (0.0135)	0.002 (0.0235)	0.012 (0.0231)	-0.060 (0.0225)*
S3	-0.061 (0.0135)*	-0.044 (0.0235)	-0.028 (0.0231)	-0.104 (0.0225)*
U2	-0.048 (0.0135)*	-0.050 (0.0235)*	-0.062 (0.0231)*	-0.034 (0.0225)
U3	-0.073 (0.0135)*	-0.050 (0.0235)*	-0.081 (0.0231)*	-0.084 (0.0225)*
B2	-0.001 (0.0135)	-0.018 (0.0235)	-0.005 (0.0231)	0.017 (0.0225)
B3	-0.057 (0.0135)*	-0.063 (0.0235)*	-0.062 (0.0231)*	-0.048 (0.0225)*
P2	-0.062 (0.0135)*	-0.061 (0.0235)*	-0.022 (0.0231)	-0.100 (0.0225)*
P3	-0.177 (0.0135)*	-0.158 (0.0235)*	-0.150 (0.0231)*	-0.213 (0.0225)*
F2	0.011 (0.0135)	0.015 (0.0235)	0.021 (0.0231)	-0.004 (0.0225)
F3	-0.053 (0.0135)*	-0.028 (0.0235)	-0.064 (0.0231)*	-0.066 (0.0225)*
Age	-0.001 (0.0011)	-0.014 (0.0041)*	0.001 (0.0041)	0.002 (0.0016)
Gender				
Female	0.003 (0.0371)	-	-	-0.033 (0.0421)
Race				
Non-white	-0.090 (0.0345)*	-0.100 (0.0573)	-0.197 (0.0758)*	-0.006 (0.0434)
Education				
Some college	0.020 (0.0479)	0.0243 (0.0776)	-0.018 (0.0768)	0.131 (0.0714)
College degree	-0.027 (0.0461)	-0.038 (0.0771)	-0.075 (0.0708)	0.081 (0.0696)
Post-graduate	0.013 (0.0488)	-0.054 (0.0833)	0.011 (0.0800)	0.180 (0.0710)*
Marital Status				
Not married	-0.038 (0.0294)	-0.006 (0.0477)	-0.115 (0.0680)	0.034 (0.0456)
Constant	0.873 (0.0800)*	1.648 (0.2395)*	0.834 (0.2681)*	0.643 (0.0998)*
Random effects				
Cons	0.145 (0.0106)	0.130 (0.0177)	0.125 (0.0168)	0.122 (0.0158)
Residual	0.155 (0.0043)	0.148 (0.0074)	0.152 (0.0073)	0.158 (0.0071)

S = Sexual function; U = Urinary function; B = Bowel function; P = Pain; F = Fear of the future
* P<0.05

Figure II-1. Distribution of Standard Gamble Utility Values for Health States

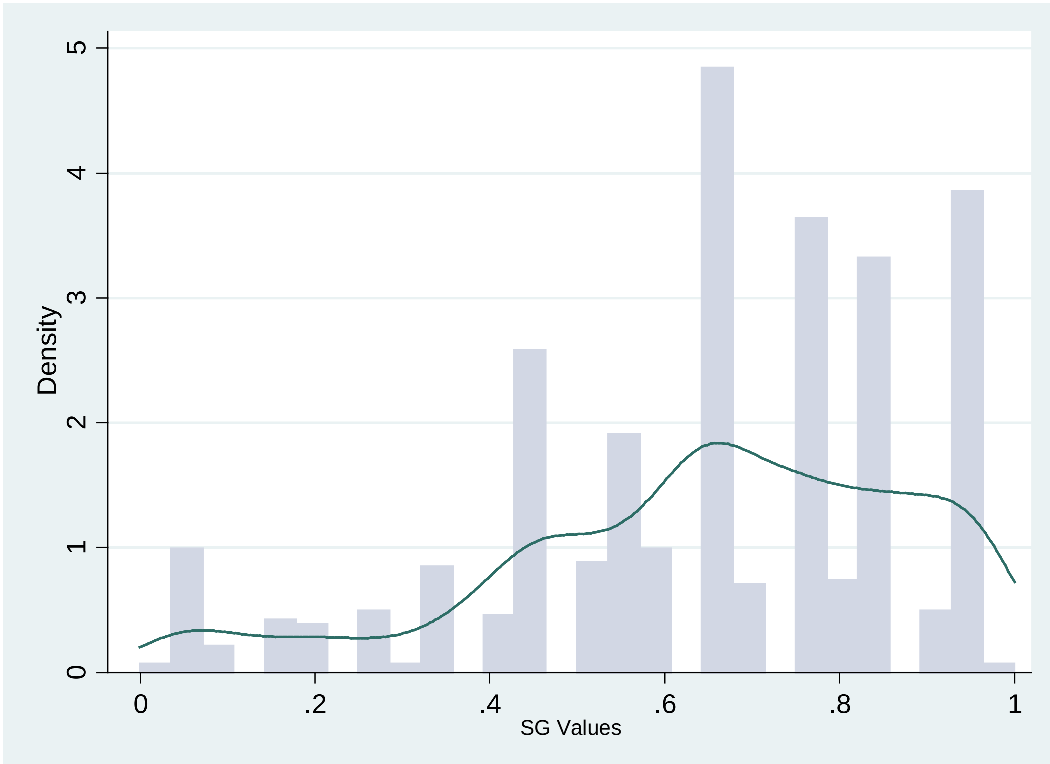
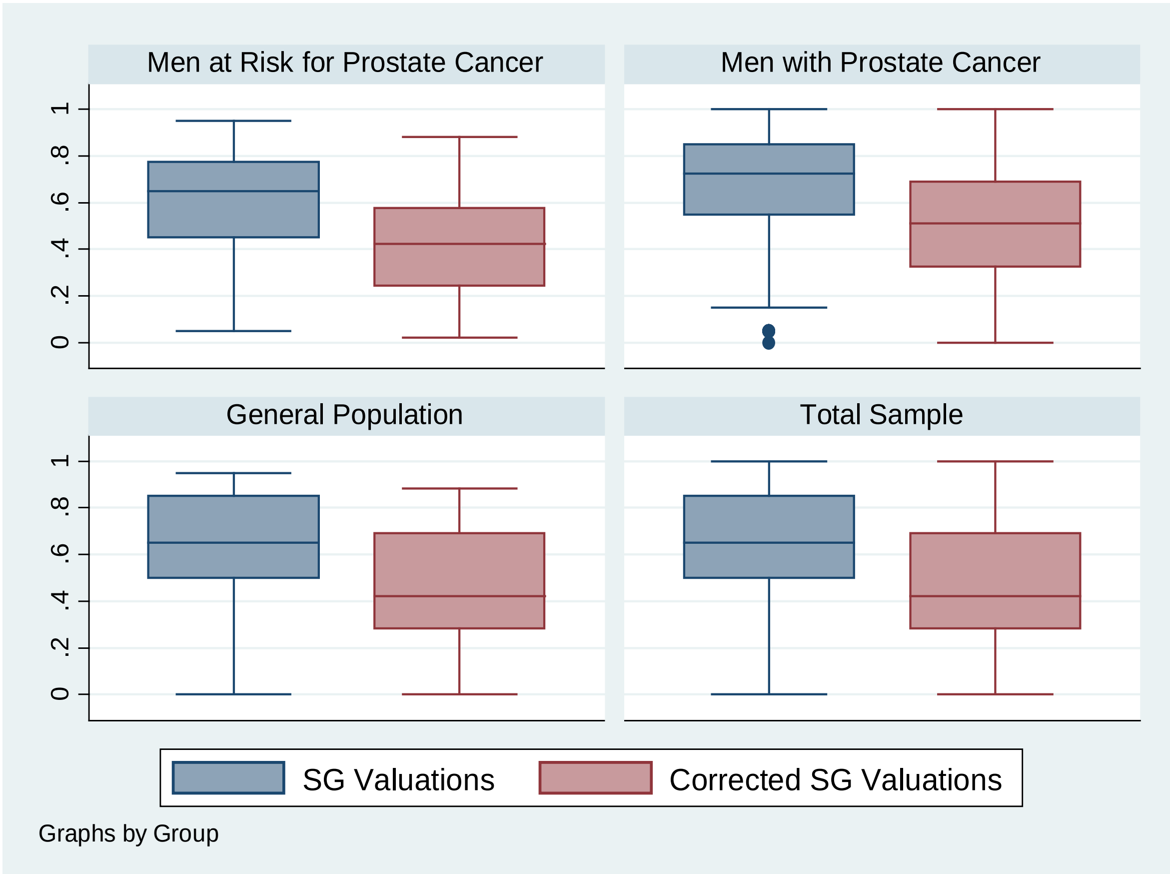


Figure II-2. Standard Gamble Health State Values with Loss Aversion Correction



Chapter III: Impact of Utility Values from Different Perspectives on the Incremental Cost Effectiveness Ratio

Abstract

Objective: To understand the impact of the utility value in a prostate cancer cost-utility model.

Methods: Utility values were derived from a cross-sectional study with three populations: men with prostate cancer, men at risk for prostate cancer, and the general population. The utility assigned to the sexual function, urinary function, and bowel function was applied to a decision tree framework, holding all other parameters constant. One-way sensitivity analysis was conducted by varying the utility value by perspective and by a decrease of 10% and 20%.

Results: The quality adjusted life year (QALY) was lowest for the general population and highest for the at-risk population. The ICER for the patient perspective was nearly identical to the ICER for the at-risk population. A 10% decrease resulted in an improved ICER by about $15,000 and a 20% decrease in utility estimate results in an improved ICER by about $30,000.

Conclusions: While the overall ICERs were high and would not be considered cost-effective, the perspective of the general population is more cost effective compared to the patient perspective.

Introduction

Cost-effectiveness models are routinely used by health policy makers to evaluate medical interventions and to allocate resources [1]. The cost-effectiveness model is used to calculate an incremental cost-effectiveness ratio (ICER), measured as the incremental cost of an intervention divided by its incremental benefits. When effectiveness is measured as utility, the model is referred to as a cost-utility analysis (CUA) where the denominator is quality-adjusted life years (QALY). A QALY is a composite value of life years remaining and the quality (or utility) of life in those years. There are several decisions to be made when developing a CUA model; such as, the model structure, model inputs, time horizon, and perspective [2]. Prior to developing the model, the researchers must decide if they want to model the cost-effectiveness of the intervention from the patient perspective, the societal perspective, or a different, unique, perspective. Once the perspective is decided upon, the costs and benefits are measured accordingly and ultimately influence the conclusions of the evaluation [3].

Ideally, a full economic evaluation should consider the costs and benefits to society; however, evaluations are often carried out from a relevant perspective such as patients or health care payer [3]. A societal perspective comprehensively accounts for all health effects and economic consequences of using a technology, which is appropriate in a country where health care is funded by a tax-based system [5]. This may not be relevant to a private health plan in the US where patients pay for their health care and coverage of technology is based in a health plan and not a country wide application.

Countries like the United Kingdom (UK), Australia, and Canada have established health technology assessment agencies responsible for assessing medical technology. One aspect these assessments are to determine cost-effectiveness relative to alternative care [4]. Cost-effectiveness is utilized less in the United States (US), given that the health care system is largely fragmented making it difficult for a centralized agency to conduct cost-effectiveness analyses that simultaneously address the needs of all parties [5]. Recommendations on coverage of new technologies are based on a defined yet arbitrary threshold [5]. A cross in this threshold implies a change in funding decision. In the UK cost-effectiveness acceptability is plausible at £20,000 to £30,000 per QALY and in the United States, the threshold is approximately $50,000 per QALY [3]. Given the high cost of cancer treatments and potential for life-prolonging interventions, a “cancer premium” has been proposed, suggesting that individuals grant cancer treatments special status and would be willing to pay more for cancer treatments than for other interventions [6].

A cost-effectiveness analysis, or a CUA, is represented by a decision tree. A decision tree maps the outcomes associated with use of the new technology in relation to the alternative, where events are separated into those requiring a choice and those occurring by chance [7]. This allows for all possible outcomes to be valued on a single coherent scale [7]. Inputs in the decision tree include the costs of each event, the outcome measure (effectiveness measure), and the probably of each event occurring. An ideal decision tree includes all important available interventions and defines and discloses the analyst’s time frame and financial perspective [8]. For an economic evaluation to be considered sound, it is necessary to test the effect of changes in the model assumptions. The use of sensitivity analyses allows one to examine how changes in soft data can influence policy decisions [7]. If altering the value of key parameters, such as the utility value, changes the conclusion of the study, it is ‘sensitive’ to those parameters and not ‘robust’ [1].

A sensitivity analysis does not measure whether all estimates were accurate but whether any errors would have a meaningful effect on the results. The effect of parameter uncertainty on the expected cost and the expected benefit is accounted for by one-way sensitivity analysis and probabilistic sensitivity analysis [1, 9]. The objective of this study is to understand the change in the ICER for a prostate cancer CUA, when applying utility values from different perspectives and conducting a one-way sensitivity analysis. The decision tree framework for the CUA model used in this analysis serves as a platform to understand the sensitivity of the utility estimate.

Methods

Utility values were derived from a cross-sectional study with three different study populations: men with prostate cancer, a representative sample of the general population, and men at risk for developing prostate cancer. Participants valued multi-attribute prostate cancer specific health states with five attributes (sexual function, urinary function, bowel function, pain, and fear of the future) using standard gamble methodology. To determine the change in ICER when utility values are applied from different populations, or perspectives, utility values were applied to an existing cost-utility model [10].

<u>Cost-Utility Model and Parameter Estimates</u>

Cooperberg and colleagues characterized the costs and outcomes associated with radical prostatectomy (RP) and radiation therapy (RT) using a comprehensive, lifetime decision analytical model [10]. A simplified version of their decision tree and the model inputs for their analysis were used as the foundation of this report. This model was selected based on the robust structure, transparency and completeness of the model inputs and common health states included in the model and valued by the study population. The structure of the decision tree was modified to only include parameter estimates for high-risk men undergoing treatment with open radical prostatectomy (ORP) and intensity-modulated radiation therapy (IMRT). The decision tree with events and outcomes is shown in Figure III-1a and Figure III-1b.

Utility values for the CUA, from the three different study populations and the pooled sample, are presented in Table III-1. Parameter estimates, excluding the utility values, came from the Cooperberg study and are included in Table III-2. The costs associated with the medical resource utilization for each treatment were calculated from the US payer perspective; for this analysis they were held constant while changing the utility value. This means that US payer costs were modeled when the utility value was from the societal perspective. This discrepancy in perspective is for this example only and to understand the sensitivity of the utility value.

Parameter Uncertainty

There are two types of uncertainly in CUA modeling: parameter uncertainly and model uncertainly [9, 11]. For the scope of this paper we only focused on parameter uncertainty, specifically the sensitivity on the utility value. Since the model structure was used as an example framework and simplified to meet the needs of this analysis, we will not be examining model uncertainty. There are two different sensitivity analyses for parameter uncertainty: one-way sensitivity analysis and probabilistic sensitivity analysis. One-way sensitivity analysis looks at a single parameter to assess the impact that changes in a certain parameter will have in the model's conclusion; in this case the utility value [12]. A probabilistic sensitivity analysis is done to vary all parameters; if the estimates of the parameters are independent of each other then the outcome can be simulated by taking random draws from each distribution and calculating the outcome variable, such as the expected utility of following a particular strategy through a decision tree

[2]. A probabilistic sensitivity analysis is not appropriate for this analysis since we want to hold all other parameters constant and only look at the effect of the utility value on the ICER.

Results

There was no statistically significant difference in disease-specific utility values between study populations, but there were slight variations in the utility values for each attribute indicating the potential for clinical significance. The utility values or disutility estimates for each perspective and for the pooled data were applied to the decision tree framework for the CUA model. This model included health states for erectile dysfunction (ED), urinary incontinence (UI), genitourinary (GU) toxicity, and gastrointestinal (GI) toxicity. The disutility for severe sexual dysfunction was assigned to the ED health state; severe urinary dysfunction was assigned to the UI health state and GU toxicity, and severe bowel dysfunction was assigned to the health state for GI toxicity.

All parameter estimates in the CUA model were held constant across perspectives except for the utility values, including the cost estimates based on the US payer perspectives. When applying the utility values of the societal perspective (general population), there is a mismatch in the perspective for the utility values and the cost. While inappropriate for CUA modeling, this was necessary for this application to single out the impact of perspective specific to the utility value. Radiation treatment had larger QALY compared to surgery [Table III-3] for each scenario. The QALY was lowest for the general population and highest for the at-risk population. While the overall ICERs were high and would not be considered cost-effective, the perspective of the general population was more cost effective compared to the patient perspective (difference of $8,354). The ICER for the patient perspective was nearly identical to the ICER for the at-risk population. Using utility estimates from the pooled data resulted in an

ICER of $243,748, which was more cost-effective than either the patient perspective or the at-risk perspective but least cost effective than the societal perspective.

A one-way sensitivity analysis was conducted on the utility estimate for all three perspectives [Figure III-2]. The utility estimate was decreased by 10% and 20%; a 10% decrease resulted in an improved ICER by about $15,000 and a 20% decrease in utility estimate results in an improved ICER by about $30,000. The utility estimate was not increased by 10% or 20% as that would be put utility greater than 1.0. A review of utility values for prostate cancer outcomes estimated a utility of severe sexual dysfunction of 0.85, severe urinary dysfunction of 0.72, and severe bowel dysfunction of 0.91 [13]. The ICER when using these estimates was $175,978, which was $70,619 lower than the ICER for the base estimates from the patient population. While this would still not be considered cost-effective, it demonstrated a significant change in ICER.

Discussion

Utility values for the same health state attributes from three different perspectives (patient perspective, societal perspective, at-risk population) were applied to an existing decision tree to understand the magnitude of change in ICER for the CUA. Using the societal perspective produced the most cost-effective result, in this example. While these results do not give guidance on the recommended perspective, the interpretation of data should factor in the perspective of the model. There was a change in ICER comparing the patient perspective to the general population ($8,354). The QALY estimate of the at-risk population was very similar to the ICER for the patient population; difference of $1,288. Since the new technology would not be considered cost-effective regardless of the utility value, it is unclear what degree of change in the utility value would shift the not cost-effective technology to cost-effective, for this example.

The one-way sensitivity analysis produced a range in ICER for the decrement in utility values. When the utility value was decreased by 20%, there was a change in ICER of approximately $30,000. With use of the utility values from the Bremner publication [13] a change in the ICER of approximately $70,000. In the context of the threshold for cost-effectiveness, a change in $30,000 and $70,000 can certainly cause a cross in threshold and change in decision-making. A similar study looked at the cost-utility of alemtuzumab for T-cell prolymphocytic leukemia, and found that changing the utility values had a moderate impact on cost-effectiveness; a lower ICER was found when using clinician derived utilities compared with then utilities for patients were assumed [14].

The National Institute for Health and Care Excellence (NICE), the appraisal committee in the UK, assesses cost-effectiveness of a new technology based on the ICER, the degree of uncertainty surrounding the calculations of ICERs, the innovative nature of the technology, particular features of the condition and population receiving the technology, and where appropriate, the wider societal costs and benefits [15]. The importance in the degree of uncertainty in parameter estimates and the calculations of ICERs was highlighted with these results. A change in utility estimate by 20% can have a sizeable impact in the ICER and depending on the calculation and threshold, an impact on decision-making. As the percentage of the population aged 80 years and older increases, decision-makers will continue to be challenged to innovate and reform how health care is provided, including ensuring affordability of drugs [16]. Health outcome and health economic researchers have the responsibility of ensuring that they are constructing cost-effectiveness models with the most accurate parameter estimates possible and using the most appropriate perspective to address the research question. A lack of due diligence can have serious implications when it comes to ensuring affordability of drugs.

There are several limitations and interpretation needs to be within the scope of the assumptions stated. First, the utility values were derived from three different populations with the intent of achieving a representative sample but was restricted to the sampling frame and to the western Washington region of the United States. Second, the decision tree and CUA foundation was modeled off of a prostate cancer CUA published in the literature. While this robust model was appropriate for the context of the study, there are several assumptions that should be acknowledged. These include: sensitivity of the utility estimates were examined while holding all other parameters constant, regardless of the perspective, and the summary of the costs were taken from the publication and not itemized in the CUA model.

The results of this analysis serve as an exploratory example to how a change in utility estimate, when comparing between perspectives and applying a one-way sensitivity analysis, could change the ICER and could potentially have a downstream impact on decision-making and funding decisions. But this is just an example and a sensitivity analysis needs to be conducted for every cost-effectiveness analysis to examine this effect within the context of the specific study objective, while accounting for the variability of every input and not just the utility value. In conclusion, selecting an accurate and appropriate utility value for use in a cost-utility model is imperative and should not be overlooked.

Table III-1. Disease-Specific and Generic Utility Values

Utility Estimate	Pooled Sample	Men with Elevated PSA	Men with Prostate Cancer	General Population
Sexual Dysfunction[1]				
Moderate	0.98	1.0	1.0	0.94
Severe	0.94	0.96	0.97	0.90
Urinary dysfunction[2]				
Moderate	0.95	0.95	0.94	0.97
Severe	0.93	0.95	0.92	0.92
Bowel dysfunction[3]				
Moderate	1.0	0.98	0.99	1.0
Severe	0.94	0.94	0.94	0.95
Pain				
Moderate	0.94	0.94	0.98	0.90
Severe	0.82	0.84	0.85	0.79
Fear of the future				
Considerable	0.95	0.97	0.94	0.93

[1] Problems achieving and maintaining an erection
[2] Problems with urination
[3] Problems with diarrhea and/or constipation

Table III-2. Cost Utility Model Parameters

Parameter Estimate	Radiation Treatment	Surgery Treatment
Health State Utilities		
Remission	0.92	0.92
Biochemical failure without hormone therapy	0.84	0.84
Biochemical failure with hormone therapy	0.78	0.78
Metastasis	0.45	0.45
Death	0.00	0.00
Probabilities		
Remission rate	56%	48.1%
Biochemical failure rate	5.63%	7.05%
Metastasis rate	16%	16%
Death from PC cancer after metastasis	12.9%	12.9%
Surgery patients in biochemical failure to receive salvage treatment	-	76%
Radiation patients in biochemical failure to receive salvage treatment	44%	-
Success of salvage therapy in returning patients to remission	50%	50%
Radiation patients receiving adjuvant hormone use	25%	-
GI Toxicity	1.6%	-
GU Toxicity	2.3%	-
ED	40%	58%
UI	-	11%

* Parameter estimates from Cooperberg et al, 2013

PC: Prostate cancer; GI: gastrointestinal; GU: genitourinary; ED: erectile dysfunction; UI: urinary incontinence

Table III-3. Incremental Cost-Effectiveness Ratio for Different Perspectives

	Patient Perspective		Societal Perspective		At-Risk Perspective	
	Surgery	**Radiation**	**Surgery**	**Radiation**	**Surgery**	**Radiation**
QALY	0.2778	0.3548	0.2642	0.3439	0.2769	0.3535
Total Cost	$10,305	$29,293	$10,305	$29,293	$10,305	$29,293
ICER		$246,597		$238,243		$247,885

* Cost estimates obtained from the Cooperberg et al, 2013 reference: US payer perspective held constant with utilities adjusted for perspective.

Figure III-1a. Outline of Cost Utility Model: Treatment Arm A

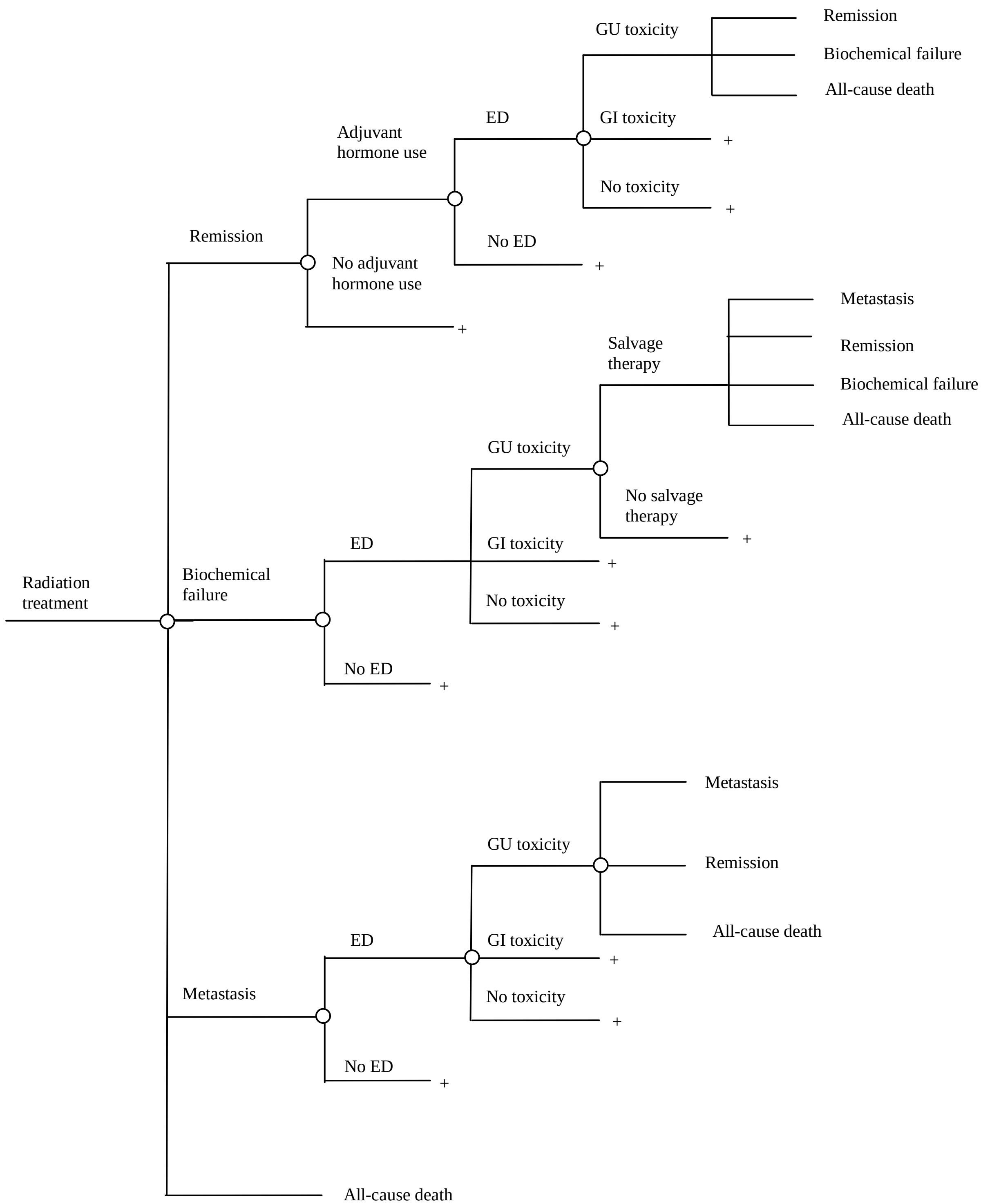


Figure III-1b. Outline of Cost Utility Model: Treatment Arm B

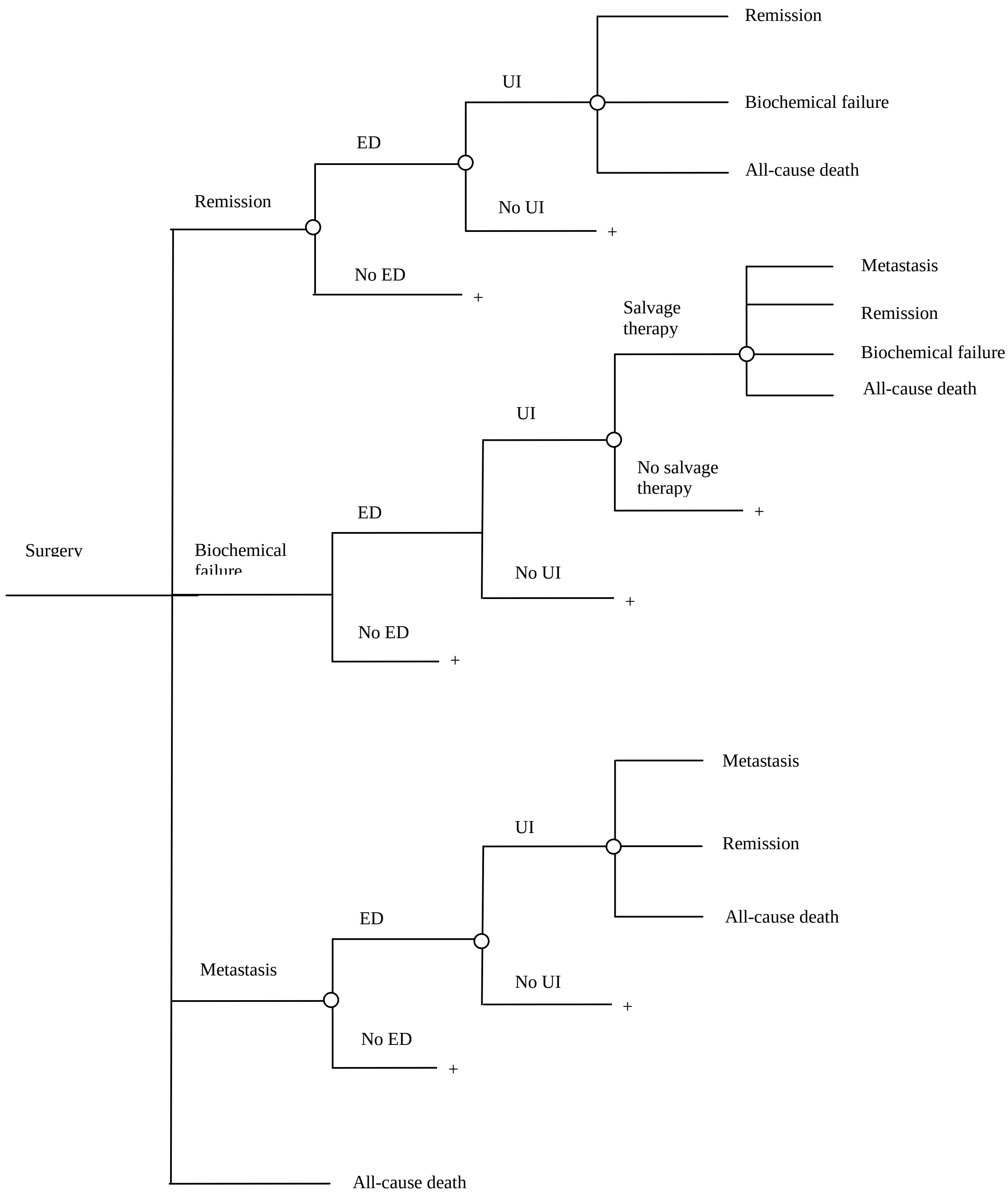
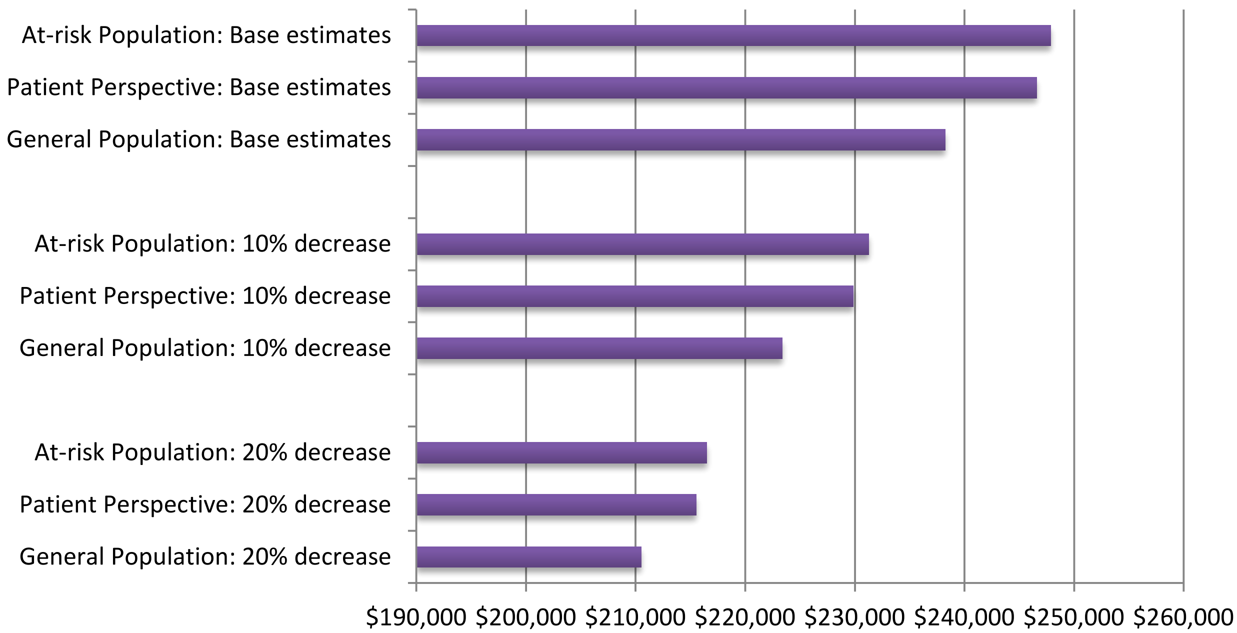


Figure III-2. One-way Sensitivity of Utility Parameter



Chapter IV: Overall Research Implications

Preference values, or utility values, have application in economic modeling to assess the incremental benefit of new technologies relative to cost. Preference values can be obtained from patients currently experiencing a certain health state, from people with past experience of that health state, close relatives of patients, health care professionals, and from samples of the general public [1]. Preference values can be elicited with direct measures, such as the SG and the TTO, or indirect measures, such as the EQ-5D or the HUI [2]. In preference elicitation studies, the researchers need to conscientiously define the health states, select the appropriate perspective, and consider the method of elicitation as these tasks influence the preference values and the valuation of health state. The societal perspective allows for comparison of utility values between disease states it does not allow for the patient experience [3]. Available evidence suggests that experience of illness may influence respondent's valuations of health states; patients with a particular condition often assign a higher utility than do patients without the condition because of adaptation to their disease state [4]. The results of this study enhance understanding of utility values from different perspectives and highlight the implications of using one preference elicitation method over another. The results show the relationship between utility values when using a disease-specific method and a generic preference method based on community preferences.

Based on the results of this study it is recommended to measure utility values for prostate cancer outcomes using the general population and a disease-specific measure. The general population, or societal perspective, allows for the comparison of utility values in relation to other diseases when they are also valued by general population group. The use of disease-specific health states valued by the standard gamble or time trade off method is imperative in prostate cancer, where symptoms such as sexual functioning, urinary functioning, and bowel function are of high importance to patients with the disease but not captured in the classification system of generic measures, such as the EQ-5D or HUI. The results of the CUA indicated that when using the societal perspective interventions may be considered more cost-effective compared to the use of the patient perspective. This is particularly important for technology appraisal agencies to consider given the funding reimbursement based on the results of a CUA.

The National Institute for Health and Clinical Excellence (NICE), the appraisal committee in the UK, assesses cost-effectiveness of a new technology based on the incremental cost-effectiveness ratio (ICER), the degree of uncertainty surrounding the calculations of ICERs, the innovative nature of the technology, particular features of the condition and population receiving the technology, and where appropriate, the wider societal costs and benefits [5]. The importance in the degree of uncertainty in parameter estimates and the calculations of ICERs is highlighted in the results of this study. Health outcome and health economic researchers have the responsibility of ensuring that they are constructing cost-effectiveness models with accurate parameter estimates, using the most appropriate perspective to address the research question, and ensure that the utility estimates are derived from the appropriate perspective and for the health states included in the model. A lack of due diligence can have serious implications when it comes to ensuring affordability of drugs.

This study highlights the importance of obtaining utility values that are relevant to the cost-utility model and considering the source of utility values when comparing across disease states and study designs. This is the first study designed to compare utility values derived from the patient perspective, the societal perspective, and a unique perspective of men at risk for developing prostate cancer. This third population is a novel addition to the study design and area of research and to our knowledge has not been previously studied. The perspective was included to capture utility values from a group that does not experience the health state, but in theory is a highly educated general population group since they have been screened for prostate cancer, have discussed prostate cancer with a physician, and the idea of experiencing the health states is a real, immanent possibility. The results indicate that this group is a valid perspective to understand; while their demographic characteristics and HUI utility values are similar to the patient group, their valuations of the disease-specific health states are more similar with the general population group. Based on the results of the regression mode for the at-risk population, using the algorithm to calculate the disease specific utility values for the health state classification system for the CUA produces an ICER very similar to the ICER for the patient perspective. While the differences are marginal, we see that this group is behaving as a separate, unique perspective and one that could have clinical meaning for health outcomes research.

Overall, there was no statistically significant difference in utility values for the 18 prostate cancer-specific health states comparing men with prostate cancer, men at risk for prostate cancer, and a general population sample. But what is important to discuss is the clinical significance of these results. The SG values trended towards the men with prostate cancer rating the health states higher than the general population and higher than men at risk for prostate cancer. In addition, the HUI utility values show that men with prostate cancer have lower HRQoL compared to the other groups. Overall the utility values for the 18 health states were high, with the data skewed towards 1.0 (most desirable state) indicating that while the prostate cancer outcomes are detrimental to patients with prostate cancer, there are other factors to life that may be more important to them than these outcomes. For prostate cancer, the outcomes are manageable yet important and clinically they need to be treated, as this study shows there is a reduction in HRQoL because of their disease state, both from the patient perspective and the perspective of men and women without prostate cancer.

The utility values for the 18 health states were used to generate a model that can be used to predict the utility values for all 243 health states in a prostate specific health state descriptive system. The three different perspectives allowed for a model specific to the population of interest and for comparison of weights and relative importance of main effects between populations. Value assigned to each level for the five attributes were slightly different between perspectives, indicating the needs for a separate algorithm for the classification system when using the different perspectives. While the utility estimates from each perspective were not significantly different, there was a change in ICER when applying the different utility values and holding all other parameters constant. Again we observe that while the results were not statistically significant, there are clinical implications. In the context of this study, the small difference in health state valuations and classification system translate into a difference observed in the CUA model. For this example, the ICER does not cross a threshold that would change decision making for a new technology, but given a potential cancer premium the fluctuations of the ICER from the sensitivity analysis a health outcomes researcher needs to critically consider the appropriate perspective and methods to derive utility.

Throughout the study there was an important discussion of sample size. The minimally important difference between mean utility values for disease specific health states in prostate cancer is unknown. The sample size was estimated based strategies conducted in similar areas of research with a hypothesized mean difference. The study enrolled the targeted number of participants for each group, but with the reduced number of health states valued by each participant, it is unclear if there was a large enough sample to detect a statistically significance difference. Despite this limitation, there were still important clinically significant trends observed in the data. And as a strategy to explore the results of the study with a larger sample size the data for each group was pooled so that each health state was valued by 40-50 participants. This exploratory strategy was considered given the similarities in the results when the algorithm was calculated to predict the utility value for the health state classification system. Using the total sample (n=792 health state valuations) we observed similar results in health state classification algorithm and with the CUA results. While the recommendation is to not pool the data for clinical reasons, the exercise supports the results that are observed with the smaller sample in each study population group.

In conclusion the objective of this study was to quantify the difference in utility values comparing three different perspectives and disease-specific health states with a generic preference measure. Then to understand the sensitivity of the disease-specific utility value derived from three perspectives in a CUA model. The utility values for men with prostate cancer support the hypothesis that patients experiencing the disease state (patient perspective) assign higher utility values to disease-specific health states. Utility values were higher when obtained by the generic, preference based measure compared to the disease-specific method. The CUA was sensitive to the change in utility value when holding all other parameters constant.

References

Introduction

1. Torrance GW. Utility approach to measuring health-related quality of life. *J Chronic Dis*. 1987;40(6):593-603.

2. Briggs A, Claxton K, Sculpher M. *Decision Modeling for Health Economic Evaluation*. New York, NY: Oxford University Press; 2006.

3. Stiggelbout AM, de Haes JC. Patient preference for cancer therapy: An overview of measurement approaches. *J Clin Oncol*. 2001;19(1):220-230.

4. Hadorn DC, Uebersax J. Large-scale health outcomes evaluation: how should quality of life be measured? Part I – Calibration of a brief questionnaire and a search for preference subgroups. *J Clin Epidemiol*. 1995;48(5):607-618.

5. Hornberger JC, Redelmeier DA, Petersen J. Variability among methods to assess patients' well-being and consequent effect on a cost-effectiveness analysis. *J Clin Epidemiol*. 1992;45(5):505-512.

6. Chapman RH, Berger M, Weinstein MC, Weeks JC, et al. When does quality-adjusting life-years matter in cost-effectiveness analysis? *Health Econ*. 2004;13(5):429-436.

7. Schackman BR, Gold HT, Stone PW, et al. How often do sensitivity analyses for economic parameters change cost-utility analysis conclusions? *Pharmacoeconomics*. 2004;22(5):293-300.

8. Brazier J, Akehurst R, Brennan A, et al. Should patients have a greater role in valuing health states? *Appl Health Econ Health Policy*. 2005;4(4):201-208.

9. Chen RC, Chang P, Vetter RJ, Lukka H, et al. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. *J Natl Cancer Inst*. 2014;106(7).

10. Smith RA, von Eschenbach AC, Wender R, Levin B, et al. American Cancer Society Guidelines for the Early Detection of Cancer: Update of early detection guidelines for prostate, colorectal, and endometrial cancers: ALSO: Update 2001 – Testing for early lung cancer detection. *CA: Cancer J for Clinicians*. 2001:51(1):38-75.

11. De Wit GA, Busschbach JJ, De Charro FT. Sensitivity and perspective in the valuation of health status: whose values count? *Health Econ*. 2000;9(2):109-126.

12. Bremner KE, Chong CA, Tomlinson G, Alighai SM, et al. A review and meta-analysis of prostate cancer utilities. *Med Decis Making*. 2007;27(3):288-298.

13. Badia X, Diaz-Prieto A, Rue M, Patrick DL. Measuring health and health state preferences among critically ill patients. *Intensive Care Med*. 1996;22:1379-1384.

14. Dorman PJ, Waddell F, Slattery J, Dennis M, et al. Are proxy assessments of health status after stroke with the EuroQol questionnaire feasible, accurate, and unbiased? *Stroke*. 1997;28(10):1883-1887.

15. Clarke AE, Goldstein MK, Michelson D, Garber AM, et al. The effect of assessment method and respondent population on utilities elicited for Gaucher disease. *Qual Life Res*. 1997;6(2):169-184.

16. Ashby J, O'Hanlon M, Buxton MJ. The time trade-off technique: how do the valuations of breast cancer patients compare to those of other groups? *Qual Life Res*. 1994;3(4):257-265.

17. Brazier J, Deverill M, Green C. A review of the use of health status measures in economic evaluation. *J Health Serv Res Policy*. 1999;4(3):174-84.

18. Krumwiede KA and Krumwiede N. The lived experience of men diagnosed with prostate cancer. *Oncol Nurs Forum*. 2012; 39(5):E443-50.

19. Jonsson A, Aus G, Bertero C. Living with prostate cancer diagnosis: a qualitative 2-year follow-up. *Aging Male*. 2010; 13(1):25-31.

20. Kazer MW, Bailey DE Jr, Colberg J, Kelly WK, Carroll P. The needs for men undergoing active surveillance (AS) for prostate cancer: results of a focus group study. *J Clin Nurs*. 2011; 20(3-4):581-6.

21. de Moraes MH, Higa R, Cordeiro SN, et al. Life experiences of Brazilian men with urinary incontinence and erectile dysfunction following radical prostatectomy. *J Wound Ostomy Continence Nurs*. 2012;39(1):90-94.

22. Harden J, Schafenacker A, Northouse L, Mood D, et al. Couples' experience with prostate cancer: focus group research. *Oncol Nurs Forum*. 2002; 29(4):701-9.

23. Pedersen VH, Armes J, Ream E. Perceptions of prostate cancer in Black African and Black Caribbean men: a systematic review of the literature. *Psychooncology*. 2012; 21(15): 457-68.

24. Torrance GW. Utility approach to measuring health-related quality of life. *J Chronic Dis*. 1987;40(6):593-603.

25. Torrance GW, Feeny DH, Furlong WJ, et al. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. *Med Care*. 1996;34(7):702-722.

26. Feeny D, Furlong W, Torrance GW, et al. Multiattribute and single-attribute utility functions for health utilities index mark 3 system. *Med Care*. 2002;40(2):113-128.

27. Singer PA, Tasch ES, Stocking C, Rubin S, et al. Sex or survival: trade-offs between quality and quantity of life. *J Clin Oncol*. 1991;9(2): 328-334.

28. Bennett CL, Chapman G, Elstain AS, Knight SJ, et al. A comparison of perspecitves on prostate cancer: Analysis of utility assessments of patients and physicians. *Eur Urol*. 1997;32 Suppl 3:86-8.

29. Matcher DB, McCrory DC, Bennett CL. Treatment considerations for persons with metastatic prostate cancer: survival versus out-of-pocket costs. *Urology*. 1997; 49(2):218-24.

30. Volk RJ Cantor SB, Spann SJ, Cass AR, et al. Preferences of husbands and wives for prostate cancer screening. *Arch Fam Med.* 1997; 6(1):72-6.

31. Albertsen PC, Nease RF Jr, Potosky AL. Assessment of patient preferences among men with prostate cancer. *J Urology*. 1998; 159(1): 158-63.

32. Chapman GB, Elstein AS, Kuzel TM, Sharifi R, et al. Prostate cancer patient's utilities for health states: How it looks depends on where you stand. . *Med Decis Making*. 1998;18(3):278-186.

33. Chapman GB Elstein AS, Kuzel TM, Nadler RB, et al. A multi-attribute model of prostate cancer patient preferences for health states. *Qual Life Res.* 1999;8(3):171-180.

34. Souchek J, Stacks JR, Brody B, Ashton CM, et al. A trial for comparing methods for eliciting treatment preferences from men with advanced prostate cancer: Results from the initial visit. *Med Care.* 2000; 38(10):1040-1050.

35. Saigal CS, C.J., Reid K, Litwin MS, Stability of time trade-off utilities for health states associated with the treatment of prostate cancer. Quality of Life Research, 2002. 11(405-414).

36. Smith DS, Krygiel J, Nease RF Jr, Sumner W 2nd, et al. Patient preferences for outcomes associated with surgical management of prostate cancer. *J Urol.* 2002;167:2117-2122.

37. Bhatnagar V, Stewart ST, Bonney WW, Kaplan RM. Treatment options for localized prostate cancer: Quality-adjusted life years and the effects of lead-time. . *Urology.* 2004; 63(1):103-9.

38. Elkin EB, Cowen ME, Cahill D, Steffel M, et al. Preference assessment method affects decision-analytic recommendations: A prostate cancer example. *Med Decis Making*. 2004;24(5):504-10.

39. Elstein AS, Chapman GB, Chmiel JS, Knight SJ, et al. Agreement between prostate cancer patients and their clinicians about utilities and attribute importance. *Health Expect*. 2004;7(2):115-125.

40. Sackett DL, Torrance GW. The utility of difference health states as perceived by the general public. *J Chronic Dis.* 1978; 31(11):697-704.

41. Boyd NF, Sutherland HJ, Heasman KZ, Tritchler DL, et al. Whose utilities for decision analysis? *Med Decis Making.* 1990; 10(1):58-67.

42. Hall J, Gerard K, Salkeld G, Richardson J. A cost utility analysis of mammography screening in Australia. *Soc Sci Med.* 1992; 34(9):993-1004.

43. Tsevat J, Cook EF, Green ML, Matcher DB, et al. Health values of the serioulsy ill. *Ann Intern Med.* 1995; 122(7):514-520.

44. Revicki DA, Shakespeare A, Kind P. Preferences for schizophrenia-related health states: A comparison of patients, caregivers and psychiatrists. *Int Clin Psychopharmacol.* 1996; 11(2):101-8.

45. Dominitz JA, Provenzale D. Patient preferences and quality of life associated with colorectal cancer screening. *Am J Gastroenterol.* 1997;92(2):2171-2178.

46. Molzahn AE, Northcott HC, Dossetor JB. Quality of life in individuals with end stage renal disease: perceptions of patients, nurses, and physicians. *ANNA J.* 1997; 24(3):325-33.

47. Jalukar V, Funk GF, Christensen AJ, Karnell LH. Et al. Health states following head and neck cancer treatment: Patient, health-care professional, and public perspectives. *Head Neck.* 1998;20(7):600-608.

48. Tsevat J, Dawson NV, Wu AW, Lynn J, et al. Health values of hospitalized patients 80 years or older: Hospitalized elderly longitudinal project. *JAMA.* 1998; 279(5):371-5.

Chapter I

1. Torrance GW. Utility approach to measuring health-related quality of life. *J Chronic Dis*. 1987;40(6):593-603.

2. Bremner KE, Chong CA, Tomlinson G, et al. A review and meta-analysis of prostate cancer utilities. *Med Decis Making*. 2007;27(3):288-298.

3. De Wit AG, Busschbach JJ, De Charro FT. Sensitivity and perspective in the valuation of health status: whose values count? *Health Econ*. 2000;9(2):109-126.

4. Stiggelbout AM, de Haes JC. Patient preference for cancer therapy: an overview of measurement approaches. *J Clin Oncol*. 2001;19(1):220-230.

5. Hadorn DC, Uebersax J. Large-scale outcome evaluation: How should quality of life be measured? Calibration of a brief questionnaire and a search for preference subgroups. *J Clin Epidemiol*. 1995;48(5):607-618.

6. Hadorn DC. The role of public values in setting health care priorities. *Soc Sci Med*. 1991;32(7):773-781.

7. Froberg DG, Kane RL. Methodology for measuring health-state preferences. III: Population and context effects. *J Clin Epidemiol*. 1989;42(6):585-592.

8. Horseman J, Furlong W, Feeny D, Torrance G. The health utilities index (HUI): concepts, measurement properties and applications. *Health Quality Life Outcomes*. 2003; 1: 54-66.

9. Ashby J, O'Hanlon M, Buxton MJ. The time trade-off technique: how do the valuations of breast cancer patients compare to those of other groups? *Qual Life Res*. 1994;3(4):257-265.

10. van Osch SM, Wakker PP, van den Hout WB, et al. Correcting biases in standard gamble and time trade off utilities. *Med Decis Making*. 2004;24(5):511-517.

Chapter II

1. Briggs A, Claxton K, Sculpher M. *Decision Modeling for Health Economic Evaluation. Handbooks in Health Economic Evaluation Series*. Oxford: Oxford University Press; 2006.

2. Rentz AM, Kowalski JW, Walt JG, et al. Development of a preference-based index from the National Eye Institute Visual Function Questionniare-25. *JAMA Ophthalmol*. 2014;123(3):310-318.

3. von Neumann J, Oskar M. *Theory of Games and Economic Behavior*. 3rd ed. Princeton: Princeton University Press; 1953.

4. Gold MR, Patrick DL, Torrance GW, et al. Identifying and valuing outcomes. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996:82-134.

5. Bremner KE, Chong CA, Tomlinson G, et al. A review and meta-analysis of prostate cancer utilities. *Medical Decision Making*. 2007;27(3):288-298.

6. Neumann PJ, Goldie SJ, Weinstein MC. Preference-based measures in economic evaluation in health care. *Ann Rev Public Health*. 2000;21:587-611.

7. Krahn M, Ritvo P, Irvine J, Tomlinson G, et al. Construction of the patient-oriented prostate utility scale (PORPUS): a multiattribute health state classification system for prostate cancer. *J Clin Epid*. 2000;53:920-930.

8. Krahn M, Ritco R, Irvine J, Tomlinson G, et al. Patient and community preferences for outcomes in prostate cancer. *Med Care*. 2003;41(1):153-164.

9. Dolan P, Roberts J. To what extent can we explain time trade-off values from other information about respondents? *Soc Sci Med*. 2002;54(6):919-929.

10. Robinson A, Dolan P, Williams A. Valuing health status using VAS and TTO: what lies behind the numbers? *Soc Sci Med*. 1997;45(8):1289-1297.

11. Rosen AB, Tsai JS, Downs SM. Variations in risk attitude across race, gender, and education. *Med Decis Making*. 2003;23(6):511-517.

12. Van Nooten FE, Koolman X, Brouwer WBF. The influence of subjective life expectancy on health state valuations using a 10 Year TTO. *Health Econ*. 2009;18(5):549-558.

13. Van Osch SM, Wakker PP, van den Hout WB, et al. Correcting biases in standard gamble and time tradeoff utilities. *Med Decis Making*. 2004;24(5):511-517.

14. Witney AG, Treharne GJ, Tavakoli M, et al. The relationship of medical, demographic and psychosocial factors to direct and indirect health utility instruments in rheumatoid arthritis. *Rheumatology*. 2006;45(8):975-981.

15. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21(2):271-292.

16. Hanley JA, Negassa A, Edwardes MD, Forrester JE, et al. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol*. 2003;157:364-375.

17. Burton P, Gurrin L, Sly P. Extending the simple linear regression model to account for correlated responses: An introduction to generalized estimating equations and multi-level mixed modeling. *Statist Med*. 1998;17(11):1261-1291.

18. Abe Y, Gee KA. Sensitivity analyses for clustered data: An illustration from a large-scale clustered randomization controlled trial in education. *Eval Program Plann*. 2014;47C:26-34.

19. Tversky A, Kahneman D. Advances in prospect theory: cumulative representation of uncertainty. *J Risk Uncertain*. 1992;5:297-323.

20. Tomlinson G, Bremner KE, Ritvo P, et al. Development and validation of a utility weighting function for patient-oriented prostate utility scale (PORPUS). *Med Decis Making*. 2012;32:11-30.

21. Zhang Y, Zhang B, Wise B, et al. Statistical approaches to evaluating the effect of risk factors on the pain of knee osteoarthritis in longitudinal studies. *Curr Opin Rheumatol*. 2009;21(5):513-519.

22. Dolan P, Gudex D, Kind P, et al. Valuing health states: A comparison of methods. *J Health Econ*. 1996;15:209-231.

23. Dominitz JA, Provenzale D. Patient screening and quality of life associated with colorectal cancer screening. *Am J Gastroenterol*. 1997;92(12):2171-2178.

Chapter III

1. Jackson CH, Sharples LD, Thompson SG. Structural and parameter uncertainty in Bayesian cost-effectiveness models. *Appl Statist*. 2010;59:233-253.
2. Gold MR, Patrick DL, Torrance GW, et al. Identifying and valuing outcomes. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.
3. Earle CC, Coyle D, Evans WK. Cost-effectiveness analysis in oncology. *Annals of Oncology*. 1998;9:475-482.
4. Clement FM, Harris A, Li JJ, Yong K, et al. Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada. *JAMA*. 2009;302(13):1437-1443.
5. Chambers JD. Do changes in drug coverage policy point to an increased role for cost-effectiveness analysis in the USA? *Pharmacoeconomics*. 2014;32:729-733.
6. Greenberg D, Hammerman A, Vinker S, Shani A, et al. Which is more valuable, longer survival or better quality of life? Israeli oncologists’ and family physicians’ attitudes toward

the relative value of new cancer and congestive health failure interventions. *Value in Health*. 2013; 16:842-847.

7. McNeil BJ and Pauker SG. Decision analysis for public health: principles and illustrations. *Annu Rev Public Health*. 1984;5:135-61.
8. Kessler JM. Decision analysis in the formaulary process. *Am J Health Syst Pharm*. 1997;15:54 Suppl 1: S5-8.
9. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford University Press; New York, NY. 2006
10. Cooperberg MR, Ramakrishna NR, Duff SB, et al. Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis. *BJU Int*. 2013;111(3):437-50.
11. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). *Lancet*. 2002;360(9334):711-715.
12. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ*. 1994;3(2):95-104.
13. Bremner KE, Chong CA, Tomlinson G, et al. A review and meta-analyis of prostate cancer utilities. *Med Decis Making*. 2007;27(3):288-298.
14. Lu L, Peters J, Roome C, et al. Cost-effectiveness of alemtuzumab for T-cell prolymphocytic leukemia. *Int J Technol Assess Health Care*. 2012;28(3):241-248.
15. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: What it is and what that means. *Pharmacoeconomics*. 2008;26(9):733-744.
16. Chabot I and Rocchi A. Oncology drug health technology assessment recommendations: Canadian versus UK experiences. *ClinicoEconomics and Outcomes Research*. 2014;6:357-367.

Chapter IV

1. de Wit GA, Busschbach JJV, de Charro FT. Sensitivity and perspective in the valuation of health status: whose values count? *Health Econ*. 2000;9:109-126.

2. Gold MR, Patrick DL, Torrance GW, et al. Identifying and valuing outcomes. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

3. Tomlinson G, Bremner KE, Ritvo P, et al. Development and validation of a utility weighting function for patient-oriented prostate utility scale (PORPUS). *Med Decis Making*. 2012;32:11-30.

4. Dolan P, Gudex D, Kind P, et al. Valuing health states: A comparison of methods. *J Health Econ*. 1996;15:209-231.

5. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: What it is and what that means. *Pharmacoeconomics*. 2008;26(9):733-744.