A Systematic Review and Meta-Analysis of Prostate Cancer Utility Values of Patients and Partners Between 2007 and 2016

Anne Magnus, Wanrudee Isaranuwatchai, Cathrine Mihalopoulos, Victoria Brown, and Rob Carter

Abstract

Background. There is widespread agreement that both the length and quality of life matter when assessing new technologies and/or models of care in the treatment for cancer patients. Quality of life for partners/carers also matters, particularly for prostate cancer. **Purpose.** This systematic review aims to provide up-to-date utility values along the prostate cancer care continuum (i.e., from prescreening through to palliative care) for use where future trial-based or modelled economic evaluations cannot collect primary data from men and/or partners. **Data Sources.** A protocol was developed and registered on the international register of systematic reviews—PROSPERO. Databases searched included EBSCO Information Services (CINAHL, EconLit, Global Health, HEED, MEDLINE Complete, PsycINFO), Cochrane Database of Systematic Reviews, Web of Science, and Embase. **Study Selection.** Study selection terms included health-related quality of life, prostate cancer, and partners or carers. **Data Extraction.** The authors identified articles published between 2007 and 2016 that provided health state utility values, with statistical uncertainty, for men with or at risk of prostate cancer and/or their partner/carers. **Data Synthesis and Results.** Study quality and generalizability of utilities was evaluated and meta-analysis conducted against prespecified criteria. From 906 original articles, 29 recent primary studies met the inclusion/exclusion criteria. We tabulate all the utility values with uncertainty, along with considerable methodological detail and patient population characteristics. **Limitations.** Utility values pertaining to carers/partners were limited to one study. **Conclusions.** Studies varied in design, measurement instruments utilized, quality, and generalizability. There is sufficient qualitative and quantitative detail for the reported utility values to be readily incorporated into economic evaluations. More research is needed with carers/partners and with newly developing prostate cancer-specific quality of life tools.

Keywords

prostate cancer, utility values, preferences, quality of life, patients, carers, economic evaluation, systematic review

Economic appraisal essentially compares resource use with outcomes achieved across two alternatives—one of which is usually current practice and the other an option for change. The aim is to optimize outcomes with available resources or minimize resource use for a given outcome. Outcomes, of course, can be measured in different ways. In health, outcomes are best measured using techniques that capture both premature mortality and morbidity outcomes, that is, "healthy life years." Again, there are various ways of capturing the length of life and the quality of those life years, but the "quality-adjusted life years" (QALYs) metric is preferred by influential

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international health technology assessment agencies in the United Kingdom, Canada, and Australia. These include the National Institute of Health and Care Excellence in the United Kingdom, the Canadian Agency for Drugs and Technology in Canada, and the Pharmaceutical Benefits Advisory Committee and the Medical Services Advisory Committee in Australia. In addition to these government agencies, the QALY has strong standing among health economists and journals that report economic evaluation results.[1,2] This article, therefore, focuses on the QALY metric.

The measurement of quality in QALYs relies on health state valuations, or preferences, for particular health states. The valuation is referred to as a "health state utility value" (HSUV) and incorporates a weighting that reflects the desirability of the described health state.[1,3] The health states can be measured "indirectly" or "directly." Indirect measurement uses instruments where the importance placed on various domains of quality of life—such as pain, anxiety, or activities of daily living—have already been preset. These are called health-related quality of life (HRQoL) instrument measures and include popular instruments such as the Euroqol Five Dimensions (EQ-5D)[4] and the Assessment of Quality of Life (AQoL)[5] suite of instruments. Determining the importance of the various domains is based on scaling procedures, such as the "standard gamble" (SG) or "time tradeoff" (TTO). With these techniques respondents are asked to select between different health states that exhibit different combinations of the quality of life (QoL) domains. With SG, the tradeoff is based on risk of adverse outcomes (including death) to establish value, while with TTO, the tradeoff is based on time spent in the various health states. Once developed, the importance weights attached to the various QoL domains are called "scoring algorithms." An important design issue for these HRQoL measures relates to who is asked to make the tradeoffs, with options ranging

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from the general community, to clinicians, to politicians, to patients. Direct elicitation techniques involve asking people to preference-weight their own health (as opposed to hypothetical states), relative to some ideal of perfect health, again using one of the scaling procedures such as SG or the TTO. Over and above how QoL is measured for patients, it is increasingly acknowledged that disease and its treatment also affects the family, partners, and carers of the affected individual.[6,7] Inclusion or exclusion of these broader QoL measures is another important design issue for researchers and decision makers who seek to measure health outcomes.

Prostate cancer is a disease affecting many men around the world. In 2012, it was the fifth leading cause of male cancer death at 6.6% with an estimated 307,000 deaths worldwide. The incidence of the cancer was much larger at over 1.1 million and is relatively higher in countries where prostate specific antigen (PSA) testing plus biopsy has become more widespread.[8] Recently reported 5-year survival rate of men diagnosed with localized disease varies with age, ranging from 85% to 95% in the United Kingdom and Australia.[9,10] Treatments are being developed and new models of care introduced that may influence the quality of life of those men and their partner/carers as they survive for an increasingly longer time following their treatment decisions.

Due to budgetary constraints in the publicly and privately funded health sector throughout the world, decision makers frequently use economic evaluations to inform policy formulation regarding the introduction and funding of new technologies. Similarly in health research, model-based economic evaluations are often conducted to supplement information from randomized controlled trials (RCTs; e.g., to model long-term effects beyond the trial, to model upscaling to national application, or to model different design parameters), and/or in place of RCTs where they are not possible, due to factors such as feasibility, ethics, or resource constraints.

Furthermore, even when possible, cognitive burden is also a consideration. When a trial of a new therapy is conducted, often the collection of health state utility preferences places an additional cognitive load on unwell patients. In these circumstances, medical researchers and health economists turn to previously published work, where utility values appropriate to their particular patient population may or may not be found.

The most recent comprehensive review tabulating prostate cancer utility values (mean and range) was conducted by Bremner et al. 11 years ago.[11] They identified that variation in values for the same health states could be explained by a number of factors, including elicitation

methods (direct or indirect), severity of health states, and the individuals performing the evaluations. Since that time, new technologies have been introduced in prostate cancer care (nerve salvaging surgery, robotic surgery, pharmacology, and refined radiology options), as well as greater understanding of the role of diet and exercise on cancer survivorship and patient well-being. A review reporting prostate cancer utility values published since 2007 is timely and will provide useful information going forward. Modelled economic evaluations over this time period have relied largely on pre-2007 utility values, which could be out-of-date and should be reevaluated reflecting current community values, treatments, health literacy, and expectations. Examples of modelled economic evaluations have been sourced from the literature; the utility values used to derive the QALYs in these models are Barocas et al.[12] and Konski et al.[13]

The Movember Foundation partnered with researchers in England, Ireland, the United States, Canada, Australia, and New Zealand to evaluate the cost and health outcomes of a range of supported self-management interventions and care models to improve the quality of life of men with prostate cancer, as well as their partner/carers,[14] known globally as the TrueNTH survivorship program. Researchers at Deakin University were commissioned in 2013 to conduct an economic analysis of a new prostate cancer care model in Australia and to assist in the development of the worldwide evaluation of the TrueNTH program. This systematic review is a contribution to that commissioned evaluation and aims to provide the most up-to-date HSUVs to assist future economic evaluations, whenever high-quality utility data are needed but cannot readily be collected. The utility values will be particularly useful for evaluation of evolving interventions designed to improve the quality of life of men with prostate cancer and their partner/carers.

More specifically, our objective is to report the HSUVs with statistical uncertainty (represented by confidence intervals, standard deviations, or ranges) and an assessment of quality arising from the estimation techniques used in each study, published over the recent 10-year period to December 31, 2016, reflecting the breadth of HRQoL along the entire prostate cancer care continuum (i.e., from prescreening through to palliative care). We will also undertake meta-analyses of the HSUVs across various studies when appropriate to do so.

Methods

A review protocol was developed and registered on Prospero with registration number CRD42017051642.

Information Sources and Search Strategy

Databases searched included the host database EBSCOhost information services (Cumulative Index to Nursing and Allied Health Literature [CINAHL], EconLit, Global Health, Health Economics Evaluations Database, MEDLINE Complete, PsycINFO), the Cochrane Database of Systematic Reviews, Web of Science, and Embase. Search terms used a combination of health-related quality of life of patients with prostate cancer and their partners or carers informed by search terms in other literature-based systematic reviews.[15] A supplementary file of search strategies is attached (Appendix 1).

Eligibility Criteria

Inclusion criteria included the following: 1) English language; 2) peer-reviewed full papers; 3) study populations based on a broad community-based sample of males with, or at risk of prostate cancer, that is, a representative sample generalizable to other populations; 4) studies reporting primary utility values for prostate cancer in adults, where the method of determination of primary utility values is reported; 5) the reported utilities were provided as mean or median values (with sample uncertainty, i.e., standard error [SE] or standard deviation [SD]); and 6) studies must report the source (questionnaire) of directly or indirectly obtained utility values.

The reported utilities that were considered appropriate for use in model-based cost-utility analyses were sourced from instruments (largely HRQoL measures) that have added utility scoring algorithms, including the EuroQol (EQ-5D),[16,17] the Quality of Wellbeing Scale (QWB, QWB-SA),[18,19] Short Form Health Survey (SF-6D, SF-12, SF-36),[20] Assessment of Quality of Life (AQoL 4D,[21] AQoL 6D,[22] AQoL 8D[23]), the Health Utilities Index (HUI2, HUI3),[24] and the Patient-Oriented Prostate Utility Scale (PORPUS).[25]

The exclusion criteria were applied hierarchically at both reading of abstracts and full article stages. Exclusion criteria included the following: 1) not a full English paper; 2) not relevant to prostate cancer (if HRQoL of multiple cancers were reported, e.g., breast, prostate, and lung cancer, the prostate cancer utilities must be separately reported); 3) no numerical mean or median utility values with sampling uncertainty reported; 4) utilities reported from a secondary reference source; 5) not peer reviewed; 6) not the most recent of multiple papers published; and 7) not collected from a broad community-based sample of males with prostate cancer.
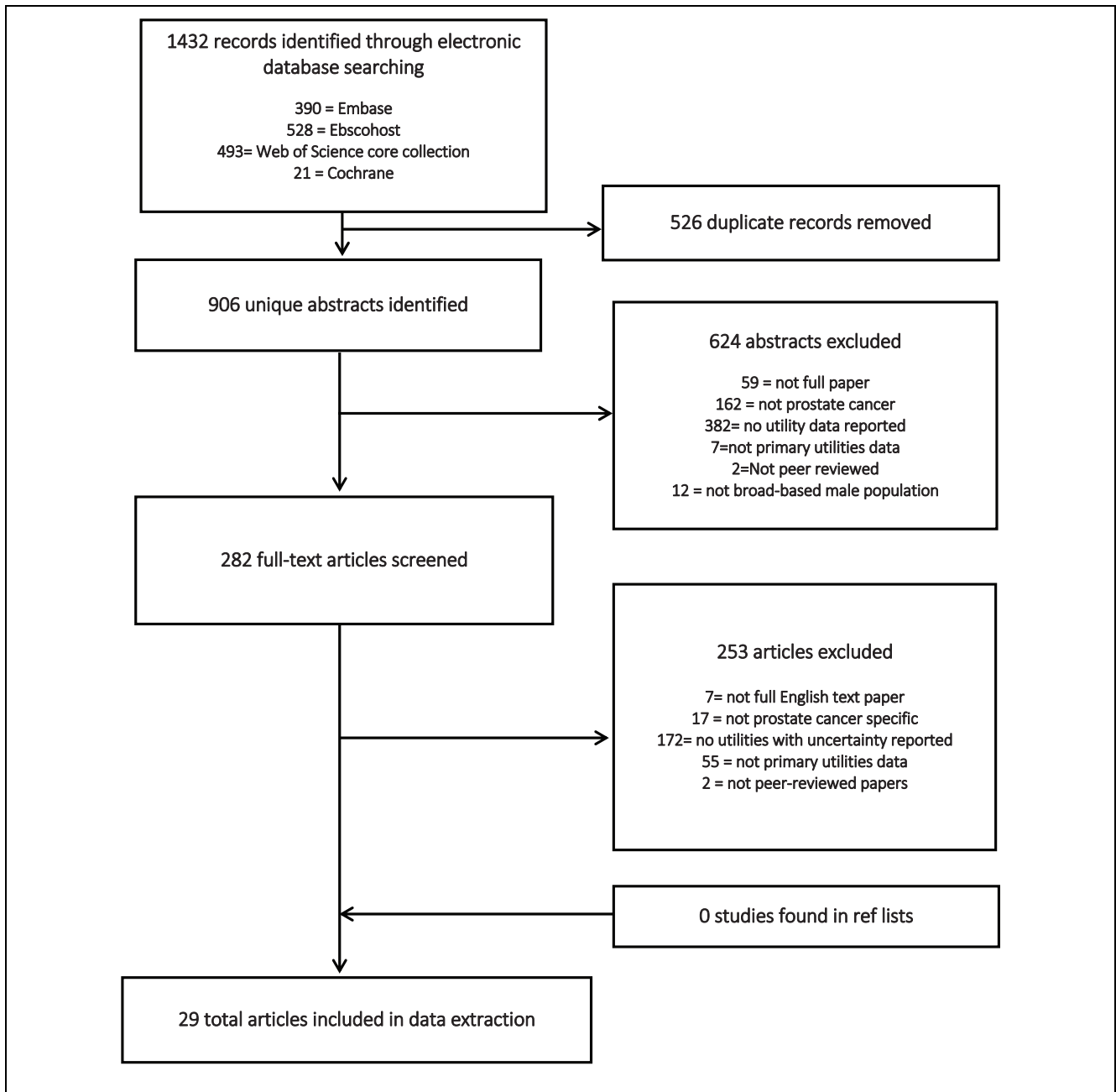
Figure 1 PRISMA flow diagram of the literature search and inclusion process.

Data Extraction and Collection Process

Two researchers, AM and WI, were involved at abstract read, with AM, WI, and RC at full read stage. CM and RC tested data extraction tools developed by AM and WI. Re-reading and classifying of articles according to inclusion and exclusion criteria were performed on 10% of abstracts by AM and WI, and agreement reached by consensus on all papers. RC and AM used the tested data extraction template. Reference lists of included studies were hand searched by AM for inclusion. All authors agreed on the final list of selected papers for extraction. The PRISMA guidelines have been used, and the PRISMA diagram is provided in Figure 1.[26]

The prostate cancer continuum we used (spanning health states of men and partner/carers from prescreening through treatments to palliation) captured the potential patients that might be included in future economic evaluations of new interventions. Studies were fitted to the prostate cancer continuum, according to the clinical characteristics of patients included, to demonstrate the breadth, depth, and potential gaps of HSUV research into this condition. *Element 1* contains studies of men in the pre-PSA screening stage. *Element 2* is made up of studies of men diagnosed, prior to treatment. *Element 3* captures studies covering the time from treatment (all types) *up to 12 months*. *Element 4* includes studies of longer term follow-up *beyond 12 mont*hs from treatment. *Element 5* includes studies of men with identified metastatic prostate cancer, and *Element 6* comprises studies of men at the palliative care stage. Studies could be classified into single or multiple elements.

Methodological Quality Assessment

There is little guidance on best practice for the systematic retrieval of HSUVs in prostate cancer, for use in economic decision models, other than the general literature on CUA methods. In most other areas of appraisal in health (e.g., clinical effect, RCTs, economic evaluations, cross-sectional observational studies, meta-analyses[27–30]), specific guidance checklists are provided for the assessment of study quality. We have noted the review studies of Papaioannou et al.,[31] Arnold et al.,[32] and Hao et al.,[33] and also been guided by quality assessments related to direct elicitation studies that do not rely on the use of validated HRQoL measures.[34] Basically, the HSUVs need to be of excellent quality, up to date, and relevant to the longer term and scope of decision analytic models envisaged.

All studies were thus evaluated for bias and generalizability according to a predefined set of criteria. Studies were expected to provide the following: 1) numerical detail of patient recruitment; 2) acknowledgement of the non-normality of the distribution of utility values; 3) clarity on the treatment of missing values; 4) discussion of the limitations and generalizability of their findings; and 5) detail on the source of funding. A score of 1 was assigned to each of these five criteria, if *not* satisfactorily met. In addition, the studies reporting indirect utility values were expected to identify the source of the utility weights (country tariff/algorithm used). Studies using direct elicitation techniques were expected to apply age-adjusted life expectancies to persons providing TTO responses. Studies providing utility values for subgroups of patients undergoing treatments (e.g., radical prostatectomy or radiation therapy) were expected to incorporate propensity weighting[35,36] to adjust the HSUVs for the potential bias introduced by low-risk patients or younger men receiving different rates of certain treatments. Dropouts occurring within a longitudinal study or RCT should have been quantified.

A summary count (maximum eight) of all potential methodological flaws was thus developed for each study according to its design and noncompliance with these expectations, summarized in Table 1. The lowest count of flaws represents the best quality reported HSUVs. All studies provided the uncertainty surrounding HSUVs, which is very important since intervention studies are not necessarily adequately powered for the precise measurement of secondary outcomes such as HRQoL.

Data Synthesis

Meta-analysis was undertaken with the Microsoft Excel add-in MetaXL version 5.3[37] using a random-effects (RE) model and a quality effects (QE) model for sensitivity analysis, adjusting for the number of flaws we identified in each study. Further sensitivity analyses were also undertaken by sequentially excluding individual studies from the meta-analyses to gauge the effect on overall results.[38] Following a set of predefined criteria, we considered a possible meta-analysis for "similar participants." The criteria included the element of the prostate cancer care continuum, the direct or indirect elicitation method, and the HRQoL instrument used. Utility values from relevant studies were included as separate observations in the meta-analyses. Forest plots are presented, and tests for heterogeneity were performed using I^2 and Cochran's Q test. Heterogeneity was regarded as substantial when I^2 exceeded 40% or the Q statistic was significant at $P < 0.10$.[39] Potential publication and small study bias was examined visually using funnel and Doi plots, where a symmetrical plot suggests no or little bias. The Luis Furuya-Kanamori index of asymmetry is also presented from the Doi plot, with an assessment of "no," "minor," or "major" asymmetry.[40]

Results

Overview of Instruments, Study Types, and Sample Sizes

A total of 906 unique reference abstracts were identified after removal of duplicates. Of these, 624 were removed at reading of abstract stage, with a further 253 removed at full reading. A total of 29 studies met the inclusion

Table 1 Quality Criteria Expected in Each Study Type

Quality Criteria/Study Type	Indirect	Direct	Subgroups Included	Longitudinal Studies
Recruitment rate	*	*	*	*
Non-normality of utility distribution	*	*	*	*
Treatment of missing values	*	*	*	*
Generalizability	*	*	*	*
Funding source	*	*	*	*
Source of tariff	*			
Age adjustment to life expectancy		*		
Propensity weighting			*	
Dropouts quantification				*

and exclusion criteria and have been incorporated in this review (see Figure 1 PRISMA flow diagram). No additional references were found by hand searching included studies. The methods used for eliciting valuations were direct (8 studies),[35,36,41–50] indirect (16 studies),[36,43,47,49,51–67] or a combination of both (5 studies).[36,43,47,49,62] The most frequently used indirect measurement instruments were the EQ-5D (13 studies),[49,53–56,60–67] the PORPUS (7 studies),[36,43,49,51,52,58,59] followed by the HUI2/3 (3 studies),[47,49,58] the QWB (3 studies),[43,49,57] the 15D (2 studies),[54,64] and the SF-36 (1 study).[62] No included studies used the AQoL instruments. Of the studies adopting the direct elicitation method, the TTO technique (9 studies)[35,41,42,44–46,48,50,62] was more frequently used than the SG (4 studies).[35,36,47,49] One study used both TTO and SG techniques.[35] There was a reasonably even spread of publications over the period, averaging almost three studies each year.

Studies were conducted in the United States (9 studies)[41,42,44–47,50,57,67]; Canada (6 studies)[36,43,49,52,58,59]; the United Kingdom (4 studies)[55,56,60,65]; multinational groups (4 studies)[53,61,63,66]; Spain (2 studies)[35,51]; Finland (2 studies)[54,64]; with one study in each of the Netherlands[48] and Japan.[62]

Most studies covered a single element of the prostate cancer continuum, while the longitudinal studies assessed up to five, including pretreatment. No study assessed all six elements. The most commonly studied area for men is posttreatment while for partners it is pretreatment (see Figure 2). The utility values varied across the continuum, with consideration being given to alternative prostate cancer treatments and common side effect profiles (impotence, incontinence, and bowel problems, with and without levels of severity).

A total of 11,401 persons were represented within the studies, of whom 10,898 were prostate cancer survivors,

194 were partners or carers of the men with prostate cancer, and 309 were either undiagnosed men or members of the general population (see Figure 3). The smallest study[42] involved 26 partners who provided personal utilities by TTO reflecting their potential HRQoL if their husband/partner was diagnosed to have specified complications of prostate cancer. A second study also involving married couples[45] compared the TTO utility valuation of potential prostate cancer outcomes for the man's health from 168 couples, taking three perspectives—the husband, the wife, and as couples. The largest multinational study[61] reported on 1,717 men with prostate cancer. The average number of participants across all 29 studies was 376.

Table 2 provides the *directly* ascertained utility values and descriptive characteristics (author/year/country, mean age of participants, sample size, tool used), sorted primarily by prostate cancer element and assigned count of methodologic flaws, then by measurement instrument applied. Studies covering multiple elements of the care continuum are placed later after studies of a single element. Table 3 provides the same descriptive characteristics of each study reporting utility values *indirectly* determined. Further details, including the patient subgroups studied, population characteristics provided, treatments given, time since diagnosis or treatment, comorbidities, symptomatology, disease staging, data collection methods, persons providing the direct elicitation values or indirect weights, the health state descriptors used, together with details of study quality assessment can be found in an Excel spreadsheet provided as a Supplementary File at the following URL: https://cloud stor.aarnet.edu.au/plus/index.php/s/evR2j022X9232Pk.

The studies were of many types varying from: 1) the evaluation of a health intervention (5 studies)[35,36,55,61,67]; 2) comparative assessments of various HRQoL measures (7 studies)[43,47–49,51,54,64]; 3) methods papers developing
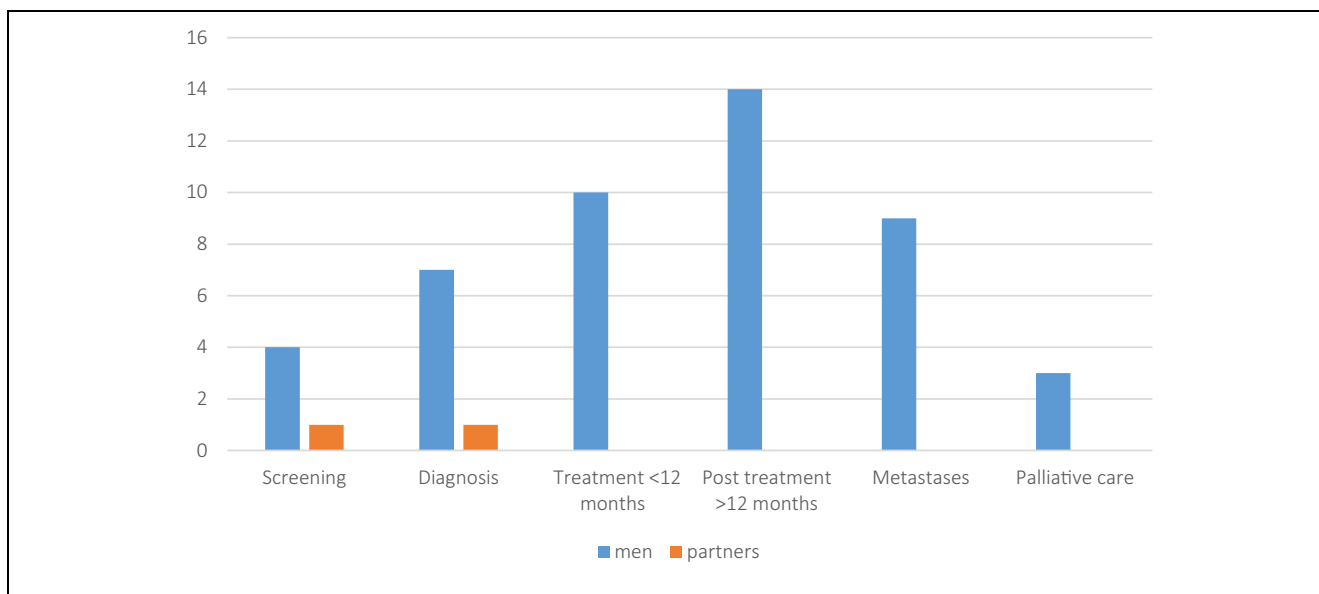
Figure 2 Studies of men and partners by element of the prostate cancer care continuum.
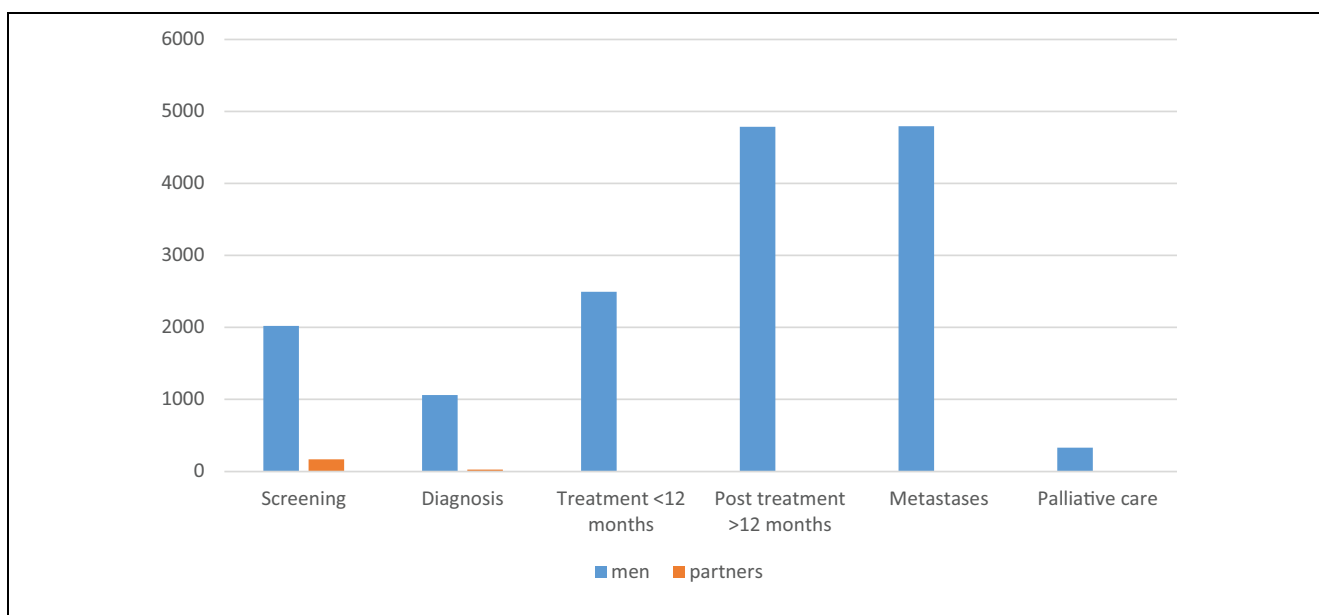

Figure 3 Study participants by element of the prostate cancer care continuum.

HRQoL prediction models (9 studies)[41,44,46,50,56–59,62]; 4) mapping studies from other non-preference-based prostate specific instruments to preference weighted utilities (4 studies)[52,53,63,66]; 5) straightforward descriptive studies (2 studies)[60,65]; and 6) limited studies of partner/carer

HRQoL assessments (2 studies).[42,45] The studies were predominantly cross-sectional (16 studies).[35,44–48,50–54,58,60,62,64,65] There were seven longitudinal,[36,49,56,57,59,63,66] three randomized controlled trials,[55,61,67] and three methods papers.[41–43]

Table 2 Studies and Published Utility Values Reporting *Direct* Elicitation Methods[a]

Prostate Cancer Element	Flaws, Max = 8	Author	Tool	Age, Mean (SD)	N	Mean HSUV (SD) for Each Health State
Single element studies						
Prescreening	2	Cantor et al[44] (2013); USA	TTO	56.4, range 45 to 70	168	*Forecasted utility values for 4 health states:* partial and complete impotence, categorized by 3 levels of importance of sexual function and 3 levels of potential adjustment to loss Partial impotence + sexual function: very important 0.83 (0.23); somewhat important 0.86 (0.20); not at all important 0.91 (0.27) Partial impotence and potential adjustment to loss: might never adjust 0.68 (0.28), bad but would adjust 0.85 (0.22), minor adjustment 0.90 (0.18) Complete impotence + sexual function: very important 0.72 (0.29); somewhat important 0.81 (0.23); not at all important 0.91 (0.27) Complete impotence and potential adjustment to loss: might never adjust 0.71 (0.30), bad but would adjust 0.84 (0.18), minor adjustment 0.93 (0.10) *Forecasted utility values for 2 levels of incontinence and 3 levels of potential adjustment to the loss* Mild to moderate incontinence and potential adjustment to loss: might never adjust 0.71 (0.30), bad but would adjust 0.84 (0.18), minor adjustment 0.93 (0.10) Severe incontinence and potential adjustment to loss: might never adjust 0.56 (0.29), bad but would adjust 0.71 (0.25), minor adjustment 0.76 (0.22)
Prescreening	3	Cantor et al[45] (2008); USA	TTO	Couples, 45–70	336	Partial impotence: H 0.84 (0.22); W 0.93 (0.14); C 0.91 (0.14) Complete impotence: H 0.76 (0.27); W 0.90 (0.16); C 0.84 (0.21) Mild to moderate incontinence: H 0.83 (0.20); W 0.91 (0.15); C 0.89 (0.15) Severe incontinence: H 0.69 (0.26); W 0.86 (0.19); C 0.79 (0.23) Urethral stricture: H 0.72 (0.27); W 0.80 (0.23); C 0.78 (0.24) Rectal injury: H 0.66 (0.29); W 0.79 (0.22); C 0.73 (0.26) Hormone-responsive prostate cancer: H 0.72 (0.27); W 0.86 (0.20); C 0.83 (0.20) Hormone-refractory prostate cancer: H 0.55 (0.28); W 0.66 (0.27); C 0.62 (0.28)
Diagnosis	5	Sommers et al[50] (2008); USA	TTO	62 (8.5)	167	Urinary incontinence: 0.906 (0.141) Erectile dysfunction: 0.923 (0.139) Bowel/rectal dysfunction: 0.859 (0.171) Metastatic prostate cancer: 0.651 (0.287)

Table 2 (continued)

Prostate Cancer Element	Flaws, Max = 8	Tool	Author	Age, Mean (SD)	N	Mean HSUV (SD) for Each Health State
Diagnosis	1	TTO	Basu et al[42] (2010); USA	57.7 (6.6)	26	Mean quality of life of partners when patients were rated in the following states: Healthy: 0.81 (na) Impotent: 0.664 (0.356) Incontinent: 0.675 (0.344) Undergone prostatectomy: 0.674 (0.324) Undergone radiation: 0.664 (0.376) Watchful waiting: 0.705 (0.327) Metastatic disease: 0.497 (0.409) Dead: 0.282 (0.340) Partner wives current health state was 0.881 (0.254)
Diagnosis	1	TTO	Dale et al[46] (2008); USA	63 (7.6)	147	Single states: Watchful waiting: 0.83 ± 0.24 Post-prostatectomy without complications: 0.80 ± 0.27; Impotence: 0.74 ± 0.29 Incontinence: 0.70 ± 0.30 Joint states: Impotence and post-prostatectomy: 0.72 ± 0.31 Impotence and watchful waiting: 0.71 ± 0.31 Impotence and incontinence: 0.66 ± 0.31
Diagnosis	2	TTO	Basu et al[41] (2009); USA	63.0 (7.6)	207	*Single states:* Impotence: 0.73 (0.30) Incontinence: 0.68 (0.32) Post-prostatectomy: 0.78 (0.29) Watchful waiting: 0.78 (0.28) Joint health states: Impotence–incontinence: 0.63 (0.35) Impotence–post-prostatectomy: 0.70 (0.32) Impotence–watchful waiting: 0.66 (0.34)
Treatment	3	PORPUS-USG	Krahn et al[36] (2009); Canada	RP = 60 (6.3), RT = 68 (6.3)	134	*RP* T1 0.96 (0.08), T2 0.87 (0.16), T3 0.91 (0.11) *RT* T1 0.93 (0.11), T2 0.88 (0.17), T3 0.88 (0.16) *Baseline scores allowing for ADT treatment pre baseline, with adjustment for age and comorbidity:* Pre baseline ADT given: 0.91 (0.02) No pre-baseline ADT given: 0.96 (0.01) *Effects of ADT concurrent with RT:* ADT started before baseline and continuing: baseline 0.90 (0.13), T2 0.86 (0.16) No ADT: baseline 0.96 (0.08), T2 0.94 (0.09)

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Table 2 (continued)

Prostate Cancer Element	Flaws, Max = 8	Tool	Author	Age, Mean (SD)	N	Mean HSUV (SD) for Each Health State
Posttreatment >12 months	2	TTO	Korfage et al[48] (2007); Netherlands	Patients 67.1 (4.3); controls 62.7 (4.3)	105	Man 1 (severe erectile dysfunction (ED) Patient (P): 0.84 (0.26), Control (C) 0.84 (0.20) Man 2 (some urinary leakage, moderate ED, moderately anxious) P: 0.76 (0.29), C: 0.79 (0.21) Man 3 (some bowel problems, moderate ED) P: 0.86 (0.23), C: 0.89 (0.13) Man 4 (serious urinary leakage) P: 0.69 (0.33), C: 0.70 (0.27) Man 5 (serious bowel problems; severe ED) P: 0.61 (0.32), C: 0.66 (0.27)
Posttreatment >12 months	4	TTO	Avila et al[35] (2015); Spain	RP 67.7 (5.2); ERT 66.9 (5.3); BrT 66.4 (5.3)	580	Preferences for treatments: RP 0.95 (0.13); ERT 0.98 (0.07); BrT 0.97 (0.10) Preferences for side effects: at 3 levels (none, slight, severe): Urinary incontinence: 0.98 (0.10), 0.97 (0.12), 0.95 (0.10) Urinary irritative/obstructive: 0.97 (0.10), 0.96 (0.13), 0.92 (0.12) Bowel: 0.97 (0.11), 0.97 (0.08), 0.98 (0.07) Sexual: 0.97 (0.10), 0.95 (0.14), 0.97 (0.08)
Posttreatment >12 months	4	SG	Avila et al[35] (2015); Spain	RP 67.7 (5.2); ERT 66.9 (5.3); BrT 66.4 (5.3)	580	Preferences for treatments: RP 0.98 (0.07); ERT 0.98 (0.10); BrT 0.98 (0.08) Preferences for side effects: at 3 levels (none, slight, severe): Urinary incontinence: 0.98 (0.09), 1.00 (0.02), 0.96 (0.10) Urinary irritative/obstructive: 0.99 (0.07), 0.97 (0.10), 0.95 (0.12) Bowel: 0.98 (0.07), 0.95 (0.14), 0.99 (0.04) Sexual: 0.98 (0.09), 0.98 (0.07), 0.99 (0.02)
Multiple element studies						
Prescreening to posttreatment >12 months	3	SG	Gries et al[47] (2016); USA	Prostate cancer 63 (5); at-risk 60 (6); general population 43 (14)	136	Eighteen health states by function (sexual, urinary, bowel, pain, well-being) and 3 severity levels reported for 3 participant groups in Table 3. Men with prostate cancer mean range 0.46–0.85 At-risk mean range 0.37–0.75 General population mean range 0.32–0.81
Diagnosis to metastatic disease	2	PORPUS-USG	Krahn et al[49] (2007); Canada	66	248	0.92 (0.12)
Treatment to metastatic disease	1	SG Prompt: PORPUS-P Marker state: PORPUS-U	Bremmer et al[43] (2007); Canada	72 (7.3)	141	Without prompts: T1: 0.85 (0.15); T2: 0.86 (0.14) With prompts: T1: 0.86 (0.15); T2: 0.86 (0.14)

ADT, androgen deprivation therapy; BrT, brachytherapy; C, couple as husband and wife; C/E, cost-effectiveness; ERT, external radiation therapy; H, husband; HSUV, health state utility value; max, maximum; NIH/NIA, National Institutes of Health/National Institute on Aging; PORPUS, Patient-Oriented Prostate Utility Scale (U, utility instrument; P, psychometric instrument); RP, radical prostatectomy; RS, rating scale; RT, radiation therapy; SD, standard deviation; SG, standard gamble; T1, time point 1; T2 time point 2; T3, time point 3; TTO, time tradeoff; W, wife.

aStudies are sorted first in order of the prostate cancer journey element, second by our quality assessment ranking, and third by the tool used. We have excluded any reference to indirect tools and started a new line whenever new utility values for new health states are provided.

Table 3 Studies and Published Utility Values Reporting *Indirect* Elicitation Methods[a]

Prostate Cancer Element	Flaws, Max = 8	Tool	Author	Age, Mean (SD)	N	Mean HSUV (SD) for Each Health State
Single element studies						
Prescreening	1	EQ-5D-3L	Lane et al[60] (2016); UK	61, range 50–69	1643	Total 0.89 (0.17) Active monitoring 0.87 (0.19) Radiotherapy 0.90 (0.16) Surgery 0.88 (0.17)
Diagnosis	1	QWB-SA	Jayadevappa et al[57] (2010); USA	RP group 59.6 (7.3); EBRT group 66.7 (7.6)	201	Baseline unadjusted RP 0.73 (0.12) EBRT 0.70 (0.11)
Treatment	3	PORPUS-U	Krahn et al[36] (2009); Canada	RP = 60 (6.3); RT = 68 (6.3)	134	*RP* T1: 0.97 (0.04), T2: 0.91 (0.06), T3: 0.94 (0.06) *RT* T1: 0.95 (0.05), T2: 0.89 (0.10), T3: 0.92 (0.07) Baseline scores allowing for ADT treatment pre-baseline, with adjustment for age and comorbidity: ADT given: 0.93 (0.01) No ADT given: 0.97 (0.0)
Treatment	5	EQ-5D	Zhang et al[67] (2016); USA	65 (7.6)	336	Baseline scores without SD provided BF + group versus Usual care adjusted mean difference 0.008, CI (−0.041, 0.058) BF + phone versus Usual care adjusted mean difference 0.016, CI (−0.033, 0.065)
Posttreatment >12 months	1	EQ-5D-3L	Glazener et al[55] (2011); UK	Intervention group 62.4 (5.8); control group 62.3 (5.6)	411	Baseline following radical prostatectomy: Intervention group = 0.797 (0.216) Control group = 0.783 (0.225) Intervention at 6 months = 0.884 (0.205) and 12 months = 0.879 (0.209) Control group at 6 months = 0.875 (0.189) and 12 months = 0.887 (0.176) Table 35
Posttreatment >12 months	3	EQ-5D-3L	Hall et al[56] (2015); UK	65 (6.6)	106	Table 6 in the supplementary data file mean and 95% CI T1: 0.840 (0.802-0.876) T2: 0.869 (0.828-0.906) T3: 0.867 (0.828-0.899) Subgroups reported without *n* Age (under and over 65), SES (IMD) Treatment types (surgery, no surgery: radiotherapy, no radiotherapy, hormone therapy, no hormone therapy) (but without *n*)
Posttreatment >12 months	4	PORPUS	Ávila et al[51] (2014); Spain	66.8 (6.4)	480	0.92 (0.09)

Table 3 (continued)

Prostate Cancer Element	Flaws, Max = 8	Tool	Author	Age, Mean (SD)	N	Mean HSUV (SD) for Each Health State
Metastatic disease	1	EQ-5D	Skaltsa et al[63] (2014); Europe	68.8 ± 7.6	209	Baseline: 0.688 ± 0.282 Week 13: 0.684 (0.27) Week 25: 0.690 (0.30) Week 37: 0.747 (0.30) Week 49: 0.799 (0.23) Week 61: 0.776 (0.15) Week 73: 0.689 (–)
Metastatic disease	4	EQ-5D	Loriot et al[61] (2015); Multinational	Not reported	1717	Baseline: intervention 0.85 (0.15); control 0.84 (0.17) Adjusted mean change from baseline to endpoint: intervention −0.07(−0.09 to −0.05); control −0.10 (−0.14 to −0.16)
Metastatic disease	5	EQ-5D-3L	Diels et al[53] (2015); Europe	72.1 (7.9)	602	All patients: 0.66 (0.01) Chemotherapy naïve patients: 0.70 (0.02) Undergoing chemotherapy: 0.66 (0.02) Post chemotherapy: 0.60 (0.03)
Palliative care	1	EQ-5D	Farrkila et al[54] (2014); Finland	75 (8.5)	30	0.551 (0.315)
Palliative care	1	15D	Farrkila et al[54] (2014); Finland	75 (8.5)	30	0.694 (0.120)
Multiple element studies						
Prescreening to posttreatment >12 months	3	HUI2	Gries et al[47] (2016); USA	Prostate cancer 63 (5); at-risk prostate cancer 60 (6); general population 43 (14)	136	Men with cancer 0.83 (0.124) At-risk 0.83 (0.168) General population 0.87 (0.136)
Prescreening to posttreatment >12 months	3	HUI3	Gries et al[47] (2016); USA	Prostate cancer 63 (5); at-risk prostate cancer 60 (6); general population 43 (14)	136	Men with cancer 0.75 (0.26) At-risk 0.77 (0.238) General population 0.84 (0.178)
Diagnosis to metastatic disease	2	HUI2	Krahn et al[49] (2007); Canada	66	248	0.87 (0.10)
Diagnosis to metastatic disease	2	HUI3	Krahn et al[49] (2007); Canada	66	248	0.82 (0.18)
Diagnosis to metastatic disease	2	QWB	Krahn et al[49] (2007); Canada	66	248	0.63 (0.13)
Diagnosis to metastatic disease	2	EQ-5D	Krahn et al[49] (2007); Canada	66	248	0.86 (0.15)
Diagnosis to metastatic disease	2	PORPUS-UI	Krahn et al[49] (2007); Canada	66	248	0.89 (0.10)

(continued)

Table 3 (continued)

Prostate Cancer Element	Flaws, Max = 8	Tool	Author	Age, Mean (SD)	N	Mean HSUV (SD) for Each Health State
Diagnosis to metastatic disease	3	15D	Torvinen et al[64] (2013); Finland	Mean: 69.4 (8.1), range 43–92	630	Loc1: 0.91 (0.09) Loc2: 0.89 (0.09) Loc3: 0.88 (0.11) Metastatic: 0.80 (0.12) Palliative: 0.67 (0.10) All patients: 0.87 (0.11)
Diagnosis to metastatic disease	3	EQ-5D-3L	Torvinen et al[64] (2013); Finland	Mean: 69.4 (8.1), range 43–92	630	Loc1: 0.90 (0.19) Loc2: 0.89 (0.14) Loc3: 0.87 (0.19) Metastatic: 0.74 (0.27) Palliative: 0.59 (0.22) All patients: 0.85 (0.03)
Treatment to posttreatment >12 months	1	EQ-5D-5L	Watson et al[65] (2016); UK	Mean 67.8 (7.6), range 46–88	316	Overall: 0.85 (0.17) Men with no moderate or big problems: Urine function: 0.87 (0.16) Bowel function: 0.86 (0.17) Sexual function: 0.86 (0.18) Men with moderate or big problems: Urine function: 0.77 (0.22) Bowel function: 0.65 (0.20) Sexual function: 0.84 (0.17)
Treatment to posttreatment >12 months	2	PORPUS-U	Ku et al[59] (2009); Canada	60.8 (7.1)	213	Mean and 95% CI: Baseline: 0.94 (0.93–0.95) 0 to 3 months: 0.81 (0.79–0.82) 3 to 9 months: 0.87 (0.86–0.89) 9 to 18 months: 0.89 (0.87–0.90) 18 to 30 months: 0.90 (0.88–0.91)
Treatment to posttreatment >12 months	5	EQ-5D	Shimizu et al[62] (2008); Japan	71.5 (6.0)	323	0.90 (0.15)
Treatment to posttreatment >12 months	5	SF-36v2 (Japanese version)	Shimizu et al[62] (2008); Japan	71.5 (6.0)	323	0.74 (0.08)
Treatment to metastatic disease	1	PORPUS-U	Krahn et al[58] (2013); Canada	72.6 (8)	585	0.91 (0.08)
Treatment to metastatic disease	1	HUI2	Krahn et al[58] (2013); Canada	72.6 (8)	585	0.85 (0.15)
Treatment to metastatic disease	1	HUI3	Krahn et al[58] (2013); Canada	72.6 (8)	585	0.78 (0.24)
Treatment to metastatic disease	4	HUI3	Bremner et al[43] (2007); Canada	72 (7.3)	141	T1 only: 0.80 (0.19)
Treatment to metastatic disease	4	QWB	Bremner et al[43] (2007); Canada	72 (7.3)	141	T1 only: 0.65 (0.13)

(continued)

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Table 3 (continued)

Prostate Cancer Element	Flaws, Max = 8	Tool	Author	Age, Mean (SD)	N	Mean HSUV (SD) for Each Health State
Posttreatment >12 months to metastatic disease	4	PORPUS	Bremner et al[52] (2014); Canada	65.8, range 46–85 validation cohort	924	Validation cohort Pretreatment: 0.96 (0.05) 6 months: 0.93 (0.07) 12 months: 0.94 (0.06)
Metastatic disease to palliative care	3	EQ-5D	Wu et al[66] (2007); Multinational	72.4 (9.0)	280	Baseline: 0.635 (0.309)

ADT, androgen deprivation therapy; BF, biofeedback; CI, confidence interval; Dev, development; EBRT, external beam radiation therapy; EQ-5D, EuroQoL-5 Dimensions; FACT-P, Functional Assessment of Cancer Therapy–Prostate; HSUV, health state utility value; HUI, health utilities index; ICED, index of co-existent disease; IMD, index of multiple deprivation; LME, linear mixed effects model; Loc1, <12 months post diagnosis; Loc2, the following 12 months; Loc3, subsequent years of remission; MAUI, multi attribute utility index; Max, maximum; OR, odds ratio; PCI, Prostate Cancer Index; PORPUS, Patient-Oriented Prostate Utility Scale (U, utility instrument; P, psychometric instrument); PROMS, patient-reported outcome measures; QoL, quality of life; QWB, Quality of Wellbeing Scale; RP, radical prostatectomy; RT, radiation therapy; SD, standard deviation; SES, socioeconomic status; SF-36, Short Form Health Survey (36 items); T1, time point 1; T2, time point 2; T3, time point 3; TURP, transurethral resection of prostate.
a Studies are sorted first in order of the prostate cancer journey element, second by our quality assessment ranking, and third by the tool used. We have excluded any reference to direct tools and started a new line whenever new utility values for new health states are provided.

Evaluation of Study and Utility Quality

Sources of funding were provided in all but one study.[62] Full funding was provided from pharmaceutical or health care industry products in four studies[53,61,63,66] as well as partial funding along with a government or cancer societies or institutes, to another four studies.[42,49,54,64] The balance of studies was fully supported by research grants from government, cancer societies, or institutes.

Of the reporting and analysis requirements applicable to all studies, only three studies[43,54,65] met all five expectations; nine studies had a single flaw[35,41,46,48,55,57,58,60,63]; 11 studies had two flaws[36,41,44,49,51–53,59,61,64,66]; five studies[45,47,50,56,62] had three flaws; and one study had four flaws.[67] After testing for the additional particular expectations applicable to relevant study types (i.e., propensity weighting for subgroups of treatments, reporting dropouts in a longitudinal study, inclusion of age-adjusted life expectancy in direct studies, population tariff mismatches), the final scores out of a possible eight flaws showed no study with zero flaws; 11 studies with one flaw[35,42,43,46,54,55,57,58,60,63,65]; five studies with two flaws[41,44,48,49,59]; six studies with three flaws[36,45,47,56,64,66]; three studies with four flaws[51,52,61]; and four studies each had five flaws.[50,53,62,67]

There was no clear link between flaws in reporting and links to industry funding of research projects, but recently published studies made up 50% of the studies with the most numerous basic flaws.

Meta-Analysis Results

Full details of meta-analyzed results (tables and graphs) are provided as a supplementary file at the following URL: https://cloudstor.aarnet.edu.au/plus/s/evR2j022X9232Pk.

Overall, the majority of comparisons showed considerable heterogeneity, even though we restricted quantitative synthesis to studies in similar populations of men using the same elicitation technique (e.g., palliative care using the EQ-5D).

Discussion

The objective of this study was to report the utilities for men and their partner/carers during the prostate cancer continuum from prescreening through to palliative care. This review aimed to provide summary information for future economic evaluations of potential interventions, particularly when new utility data cannot be collected from patients. Results from both the systematic review and the meta-analyses are presented as a catalogue of

values for use at the discretion of potential users. There was considerable variability in the extent of coverage in the published literature of the elements of the continuum, the HRQoL methods and instruments, the patient groups more widely reported, and those that have received little attention. Australian and New Zealand men were underrepresented in this area. The personal HRQoL of partners/carers has been studied only once. The elements of prescreening and palliative care have received the least attention. AQoL derived utilities have not been published in this population, while the SF-6, QWB, 15D, and SG techniques were infrequently used over the period. The EQ-5D remained dominant, closely followed by the increasing use of the PORPUS. We would expect this trend to continue with increasing interest in disease-specific HRQoL instruments. The results of the meta-analyses showed that despite restricting quantitative synthesis in like populations using the same instruments there was considerable unexplained heterogeneity.

The findings of this review also show that the utility values reported by men with prostate cancer, particularly advanced disease, are lower than values in the general population. For example, McCaffrey et al.[68] reported the population norms for the EQ-5D-5L for a general South Australian population and found that the average values in men aged 65 to 74 is 0.87, whereas EQ-5D values reported in the current review, particularly in more advanced disease, are lower than this. This shows that men with advanced prostate cancer do have substantial disease burden as measured by preference-based measures. Therefore, the results of our study are not only useful to inform economic evaluations that can then be used for resource allocation decisions and policy decisions, but also are descriptive of the potential disease burden associated with the varying stages of disease.

Comparison With the Literature

Our findings concurred with Brazier et al.[69] and Bremner et al.,[11] who both found that variation in values for the same prostate cancer health states could be explained by the following: 1) elicitation methods (direct or indirect); 2) severity of the health states; and 3) the individuals performing the evaluations. To this list, we would add the following: 1) the hypothetical or realistic nature of a TTO/SG; 2) the perceptions of partner/carers, which have only recently been studied; and 3) the tools used to indirectly elicit the valuation.

While there was some overlap in the period covered between a review conducted by Torvinen et al. in 2016[70]

and this article, major differences existed in search methods, emphasis, analysis, and applicability. Torvinen et al.[70] gathered studies of HRQoL of men with prostate cancer, between 2002 and 2015. The authors did not report the actual HSUVs nor the uncertainty around the mean values, and did not evaluate the quality of the elicitation process within the studies. They restricted their searches to meta-analyses, systematic reviews, RCTs, and observational studies only, thereby excluding methods papers and mapping studies. They also did not consider partners/carers and men at prescreening or prediagnosis stages. Their review included a different range of instruments, including VAS, which does not generate a preference weighted utility between 0 and 1. They excluded any prostate cancer specific tools (PORPUS) without explanation. They did not include nor discuss the usefulness/limitations of potential meta-analysis to future modelers of interventions for improving the quality of life of men with prostate cancer. Ten of their 33 studies were published pre-2007, which we excluded since they were published before the Bremner et al. systematic review.[11] Eight of their included studies we excluded on the basis of either foreign language, absence of a summary utility score, no uncertainty estimates, or a prostate cancer specific utility score (Ruland et al.[71] combined the HRQoL of breast and prostate cancer patients). The Torvinen et al. review identified one observational study of 20 patients where the Turkish version of the 15D was reported,[72] which our search strategy failed to retrieve because we had not specifically nominated the 15D for inclusion.

Strengths

The systematic review gathers together the values that have been reported in the literature recently, providing synthesis of suitable reported values through our meta-analysis estimates. Generalizability of these utilities in future modelling evaluations or trials of prostate cancer patients is a fundamental criterion for the modelers to assess. Sufficient detail of the patient sample needs to be taken into account, including ethnicity, age, stage of disease, treatments, time since diagnosis, and quality of life before treatment. By placing our findings on the prostate cancer continuum and reporting comprehensive details in the Supplementary files, we believe we have made a valuable contribution to future economic evaluation and priority setting. The mapping studies have also provided useful examples of the degree of predictive association between the HRQoL utility values and scores on alternative prostate cancer disease specific instruments. While

helpful, these studies have been limited by small convenience samples and limitations of the statistical modelling techniques used (e.g., statistical models based on normal variable distributions have been applied to non-normal distributions of utility values without appropriate adjustments), thus potentially underestimating the uncertainty surrounding the utility values.

Rigor and reliability of the estimates is another major consideration for users of HSUVs. To address this point, we have assigned each study a summary ranking on trustworthiness of their methods to overcome or identify inherent bias within the study population. All observational studies have inherent patient self-selection bias, with patients who are less well and without higher levels of education, or access to computer assisted technologies, least likely to participate in research. Propensity score methods are being developed to adjust for treatment bias, since radical prostatectomy is offered to younger patients and brachytherapy offered to those at lower risk,[35,36] but these weighting techniques have not yet been adopted by all studies reporting on treatment subgroups. There is room for improvement in basic reporting of potential sources of bias and generalizability of study findings, when only 10% of studies in this review met all five technical criteria we considered.

Limitations

This study has some limitations that future researchers could build on. Clear guidelines to assess the quality of the HSUVs developed in studies are missing from the literature. We based our criteria around studies being up to date—their relevance and technical rigor as set out above. We believe our assessment is useful for end users, but acknowledge it is based on our experience in the conduct of economic evaluations over many years rather than widely accepted guidelines.

We focused on papers in the English language, did not include as a search term "disutility," "HRQoL," or "person tradeoff" and did not explore the grey literature; however, our methods aimed to capture the majority of the literature reporting primary HSUVs for prostate cancer.

Conclusions

This review reports methodological and qualitative details on the studies included to alert future decision analytic modelers which readily available utility values to use with confidence in their study population. The findings also alert prospective researchers regarding the need to collect further HRQoL information in the course of a trial if their patient population has not been adequately assessed in the last 10 years.

Carers have only recently become the focus of HRQoL studies and more work is needed to adequately assess the impact of prostate cancer on them. Spillover effects of prostate cancer treatments on partners are very relevant in intimate co-dependent relationships, representing important elements to consider in inclusion/exclusion decisions on the costs and outcomes measured in economic evaluations.

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