Methods for modelling the cost-effectiveness of interventions for prostate cancer: a systematic review

Protocol

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Background

Prostate cancer has the second highest incidence of any cancer in England, and the highest for males,[i] with around 40,000 new cases each year.[1] Significantly more people are diagnosed with prostate cancer than die from it, but it nevertheless leads to around 10,000 deaths per year.[1] It is primarily a disease affecting older males, with over half of new diagnoses being in those aged 70 and over.[1]

Risk factors for prostate cancer include race (higher risk amongst black males, lower risk amongst Asian males), genetic factors (including hereditary cancer syndromes, particularly with *BRCA2*, *MLH1* or *MSH2* pathogenic variants), weight and height.

There is no screening programme for prostate cancer in the UK. Well conducted systematic reviews and randomised controlled trials (RCTs) have found no impact on long-term mortality.[4, 5] The US Preventive Services Task Force has recommended against PSA-based screening for prostate cancer in males aged 70 years and over, and has said that for males aged 55–69 years the decision should be an individual one.[6]

Symptoms of prostate cancer are non-specific and are more likely to be caused by other conditions, such as benign prostate hyperplasia; they include: more frequent and/or difficult urination, increased urgency and leaking. Less common symptoms are erection problems and blood in urine or semen. In England, around half of prostate cancers are diagnosed following a two-week wait (TWW) urgent referral from a general practitioner (GP) with suspicion of cancer, while around a third result from other GP referrals.[2, 3] GPs may offer a prostate specific antigen (PSA) test or a digital rectal examination (DRE). In specialist clinics, diagnostic tests include transrectal ultrasound (TRUS) and biopsy.

[i] Throughout this protocol, male/female refers to sex (biological) while man/woman applies to gender (social)

Treatments for prostate cancer depend on a number of factors, including the position and stage of the cancer. In some cases treatment may not be initiated immediately, but the cancer monitored instead (termed active surveillance or watchful waiting). Early prostate cancer may be treated with surgery or radiotherapy, and potentially with hormone therapy. More advanced cancer may be less amenable to surgery, and may be treated with chemotherapy.

Weight and diet may be modifiable risk factors for prostate cancer, but other interventions for risk reduction have not proved effective. Finasteride and dutasteride have been investigated as chemoprevention in two placebo-controlled randomised trials, which found that although the agents reduced the overall incidence of prostate cancer, they did not lower the risk of more aggressive cancers (and increased the risk in the case of finasteride), did not reduce mortality, and had notable side effects, including erectile dysfunction, loss of libido and gynecomastia.[7, 8]

As prostate cancer is very common, and it leads to morbidity, mortality and costs to health and social care services, it is important that decisions around prostate cancer are evidence-based and consider the resource impacts on health services. Additional money spent on identifying or managing prostate cancer is money which cannot be spent on other health care activities, which may produce better outcomes for patients. This is true in publicly funded and private insurance based health care systems.

Cost-effectiveness analyses evaluate the additional costs associated with interventions as well as their health consequences. In many cases the health consequences are measured in quality-adjusted life years (QALYs) so that they can be compared across different disease areas and intervention types. If the incremental cost-effectiveness ratio (ICER, the ratio of additional costs to additional benefits) is less than a threshold, the intervention is considered to be cost-effective.

Cost-effectiveness analyses can be based on trials, in which costs and health outcomes are measured for participants with a long duration of follow-up, however this is costly and time consuming, so in many cases mathematical models are used to extrapolate results into the future, as well as to incorporate evidence from multiple sources.

Whole disease modelling is an approach which makes it possible to evaluate the cost-effectiveness of different interventions affecting different aspects of the disease pathway. It achieves this by modelling the whole disease pathway for individuals.[9] For example, it makes it possible to compare a screening programme to a treatment option. Whole disease models take into account the downstream effects of interventions, and can even be used to

evaluate different portfolios of interventions, in order to identify the most cost-effective combination of interventions.

Whole disease models are more challenging to conceptualise, build and parameterise than models of a single point of intervention, but these more focussed models can offer valuable insights for the development of a whole disease model.

We do not believe that there is any comprehensive review of economic models in prostate cancer, although a review by Sanghera et al.[10] has reviewed economic models of screening interventions for prostate cancer.

Aims and objectives

The aim of the project is to identify and bring together all health economic modelling studies in prostate cancer, to inform the development of a whole disease model for prostate cancer.

Note: It is not the aim of the project to identify parameters for the development of the whole disease model or to estimate the cost-effectiveness of any interventions for prostate cancer in any setting from the literature.

The objective of the project is to conduct a systematic review of model-based economic evaluations in prostate cancer, including a narrative synthesis.

Methods

This protocol will be deposited in the University of Exeter institutional repository (ORE) prior to the study selection component of the review.

Study identification

The strategy for identifying studies will include searches of electronic bibliographic databases (and backward citation tracking on included studies (i.e., searching the reference lists of included studies). The websites of the National Institute for Health and Care Excellence (NICE) and the UK National Screening Committee will also be searched for technical reports relating to prostate cancer. Any existing systematic reviews of economic evaluations in prostate cancer which include modelling studies will be noted and their reference lists also scrutinised.

Study selection

Two or more researchers will independently examine titles and abstracts for potential eligibility for inclusion. Disagreements will be resolved by discussion between the researchers. A random sample of 100 titles and abstracts will be used to pilot the inclusion criteria and to improve concurrence between reviewers.

Full text articles will be retrieved where reviewers agree the article may be eligible for inclusion or when there is no consensus. Two or more researchers will independently examine the full text articles to determine eligibility for inclusion. Disagreements will be resolved by discussion between the researchers with the involvement of an additional reviewer if necessary.

Table 1: Inclusion criteria for the systematic review

Criteria	Include	Exclude
Population	Males with prostate cancer Males with symptoms that may indicate prostate cancer Males with risk factors for prostate cancer Males (generally) at risk of prostate cancer	
Interventions and comparators	Interventions to manage prostate cancer Interventions to improve the diagnosis of prostate cancer Surveillance for prostate cancer Screening interventions for prostate cancer Interventions to reduce the risk of prostate cancer	Studies with a single arm (i.e., no comparator)
Forms of economic evaluation	Cost-effectiveness analyses Cost-utility analyses Cost-consequences analyses Cost-benefit analyses (where health consequences are valued in monetary units)	Cost studies Cost-minimisation analyses Preference-elicitation studies Economic burden studies Reviews of economic evaluations
Study designs	Model-based economic evaluations, including (but not limited to): decision trees, cohort models (Markov cohort simulation and partitioned survival analyses), simulation methods (Markov microsimulation, discrete event simulation, agent-based modelling, system dynamics), and hybrid models	Economic evaluations not using modelling, such as economic evaluations based solely on trial data
Other		Studies only published in abstract form

Data abstraction

Two or more researchers will independently complete data abstraction of the included studies into pre-designed templates. The items for data abstraction will be focussed on

methodology, and will not include the results of the included studies. A random sample of five studies will be used to pilot the data abstraction templates to improve concurrence between reviewers and to identify any need for modifications to the templates.

Critical appraisal

Critical appraisal is typically conducted in systematic reviews of economic evaluations so that the results from different studies can be weighed against their internal validity (risk of bias). This review is focussed on the methodology used in existing modelling studies, and will therefore include a selection of items from the Philips model checklist.[11, 12]

Data synthesis

Narrative synthesis will be conducted, supported by tables of study characteristics. Studies will be divided according to their part in the prostate cancer pathway (e.g., prevention, diagnosis, early stage treatment, late stage treatment).

Analysis

A health economist with experience of cost-effectiveness modelling and systematic review will analyse the results of the review to draw conclusions to support future development of a whole disease model and to identify any areas where further research is needed to support modelling.

Reporting

The systematic review will be reported in an article submitted to a suitable journal, and will follow the PRISMA guidelines for reporting systematic reviews.

References

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Appendix 1. Sample search strategy (MEDLINE)

1. exp Prostatic neoplasms/
2. (prostat$ adj3 (cancer$ or carcinoma$ or tumor$ or tumour$ or malignan$ or neoplas$)).tw.
3. (gleason adj3 (grad$ or scor$)).tw.
4. or/1-3
5. exp "Costs and cost analysis"/
6. (model adj3 (economic or cost)).ti,ab,kw.
7. (cost adj3 (effect$ or util$)).ti,ab,kw.
8. (economic adj3 (anal$ or eval$)).ti,ab,kw.
9. natural history model.ti,ab,kw.
10. screen$ model$.ti,ab,kw.
11. disease progression model$.ti,ab,kw.
12. or/5-11
13. 4 and 12