ESTIMATING THE BENEFITS AND HARMS OF PSA TESTING IN THE AUSTRALIAN CONTEXT

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Abstract

Results from international randomised controlled trials have been inconsistent as to whether prostate specific antigen (PSA) testing is associated with a mortality benefit. However, the PSA test is commonly used to test asymptomatic men for prostate cancer in Australia. The harms, including additional diagnostic evaluation and exposure to treatment regimens and their side-effects, may be substantial. It is possible that less frequent testing, a clearly identified target population and careful consideration of thresholds and triage protocols for men with elevated PSA could be used to achieve a more advantageous balance between the benefits and harms of testing. It is not practical to assess a wide range of potential testing strategies via clinical trials, since any testing-associated benefits for prostate cancer-specific mortality would take years to accrue and would also be logistically challenging. Furthermore, the benefits, harms and cost-effectiveness of testing in Australia depend on several factors specific to the local context, including testing uptake and the risk profile of the population. Mathematical modelling will therefore play an important role in synthesising the data from international trials with known local testing, disease and treatment variables. Here, we review the international literature on models of PSA testing and conclude that investment in a carefully calibrated and validated population model of prostate cancer in Australia will provide an important platform for estimating the impact of future candidate strategies for testing for prostate cancer.

Results from international randomised controlled trials have been inconsistent as to whether prostate specific antigen (PSA) testing is associated with a prostate-cancer specific mortality benefit. Although the European Randomised Study of Screening for Prostate Cancer (ERSPC) reported a significant 21% relative reduction in prostate cancer-specific mortality in men aged 55-69 years over 11 years of follow-up,[1] the US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial found no evidence of a mortality benefit for organised annual screening compared with opportunistic screening over 13 years of follow-up.[2] The National Health and Medical Research Council PSA Testing Expert Advisory Group recently prepared an evidence evaluation report based on a systematic review of prior systematic reviews, and concluded that "…the present evidence is inconsistent as to whether there is an effect of PSA testing, with or without digital rectal examination (DRE), on the risk of prostate cancer-specific mortality compared with no PSA testing, although the possibilities of no effect or a small protective effect cannot be excluded" and that "PSA testing with or without DRE has no discernible effect on all-cause mortality compared with no PSA testing."[3]

A study in NSW found that the annual number of PSA tests more than doubled between 1996 and 2006.[4] There was a sustained increase in prostate cancer incidence after PSA testing was introduced, presumed due in part to the effect of PSA testing uptake on increased detection. Although a decrease in incidence of advanced disease at diagnosis and a decrease in mortality from prostate cancer were also observed, factors other than PSA testing could not be excluded as potentially having an influence on these trends.

The harms of PSA testing, including additional diagnostic evaluation and exposure to treatment regimens and their side-effects, may be substantial. For example, an Australian study found that treatment for localised prostate cancer can have severe and persistent effects on quality of life, which, depending on treatment type, can involve sexual dysfunction, poor urinary function and compromised bowel function.[5] The balance of benefits and harms of any cancer testing or screening regime critically depends on several factors, including the characteristics of the test itself, the test threshold used, the frequency of testing, the age range of individuals tested (including setting a recommended upper age limit and/or using 'exit testing' to define a group at low risk of disease who do not require further testing), and the process for further triaging test-positive individuals before referring to further diagnostic evaluation. There are a range of other unanswered questions in relation to optimising prostate cancer detection, surveillance and treatment. It is possible that less frequent PSA testing

than would appear to currently exist, potentially combined with a more limited age range of screening and clearer recommendations for thresholds and triage protocols for men with elevated PSA, could be used to achieve a more advantageous balance between the benefits and harms of testing and its sequelae. There is also a potential independent role for DRE for screening, but this has not been examined in population-based studies. There are also a number of critical unanswered questions relating to the relative benefits of active surveillance compared to immediate treatment of men with a positive biopsy after an elevated PSA test, and the role and relative benefits and costs of various triage strategies for men with abnormal PSA tests (potentially including use of DRE, repeat PSA testing, assessing the rate of PSA increase, or use of magnetic resonance imaging). In addition, there are outstanding questions relating to the optimal testing and/or management of men with a family history of prostate cancer.

It is not practical to assess a wide range of potential PSA testing strategies via clinical trials, as any testing-associated benefits for prostate cancer-specific mortality would likely take years to accrue.[6] Furthermore, the benefits, harms and cost-effectiveness of testing in any particular context depend on factors specific to the local context, including testing uptake and the risk profile of the population. Therefore, mathematical modelling plays a key role in synthesising the data from international trials with local factors and simulating the effects of potential new strategies for testing or surveillance.

Models of PSA testing

Two international groups, the Fred Hutchinson Cancer Research Centre (FHCRC) and the Microsimulation Screening Analysis (MISCAN) group, have developed detailed population-based prostate cancer and PSA testing models for North America and the Netherlands, respectively. The FHCRC prostate cancer model is a comprehensive micro-simulation (individual-based simulation) of prostate cancer incidence and mortality. It has been used to evaluate the effectiveness of different PSA screening strategies in the US and the cost-effectiveness of PSA screening in British Columbia, Canada.[7,8] The disease natural history structure includes both preclinical and clinical states characterised by cancer stage and differentiation grade. The mortality component of this model uses age, stage and grade specific survival to model prostate cancer death; in the case of loco-regional cancers, survival also depended on primary treatment (radiation or surgery). PSA levels in simulated individuals are explicitly modelled as a continuous function, although other specific risk factors are not considered. Although the opportunistic PSA screening occurring in the US was taken into account when calibrating the model to US cancer incidence, realistic levels of PSA testing uptake rates (including less than 100% uptake at a distribution of times around the recommended interval) have not been used in the reported evaluations of PSA testing using the FHCRC model to date. Some of the specific harms of testing (short-term and long-term treatment effects) are taken into consideration.

In the FHCRC evaluation of PSA testing effectiveness in the US, the risk of prostate cancer death was estimated to be 2.86% in the absence of screening. A reference strategy that screens men aged 50-74 annually with a PSA threshold for biopsy referral of 4 µg/L was found to reduce the risk of prostate cancer death to 2.15%, with risk of overdiagnosis of 3.3%. A strategy that screens biennially with longer intervals for men with low PSA levels was predicted to achieve similar risks of prostate cancer death and overdiagnosis, but reduced total tests by 59% and false positive tests by 50%.[7] In the follow-up Canadian cost-effectiveness analysis, the incremental cost-effectiveness ratio of regular PSA testing was $36,300 per life-year saved, for testing every four years from ages 55 to 69 years, which indicates that this strategy is likely to be cost-effective. However PSA testing every two years, from ages 40 to 74, was associated with an incremental cost-effectiveness ratio of $588,300 per life year saved, which is very cost-ineffective. The findings were very sensitive to whether quality of life aspects were included in the evaluation, and if so, how these were weighted.[8]

The MISCAN prostate cancer model also involves a micro-simulation of prostate cancer incidence and mortality. It has been used to simulate health outcomes and corresponding costs for a cohort of men and to estimate quality of life effects for men with various PSA testing strategies.[9,10] The disease natural history structure includes both preclinical and clinical states, characterised by cancer stage and differentiation grade. Survival is modelled by age, stage and grade, and in the case of loco-regional cancers, as treatment-specific. No specific risk factors are included. In this model platform, PSA testing and biopsy are modelled as a single testing process with test characteristics (sensitivity and specificity) being stage and grade specific, and European Randomised Study of Screening for Prostate Cancer data used to inform modelling of PSA testing effectiveness. Again, realistic testing uptake assumptions have not been specifically taken into account to date, but specific harms (short-term and long-term treatment effects) are taken into consideration. Using the MISCAN platform, a recent evaluation found that PSA testing of all men between the ages of 55 and 74 would result in more life-years gained, however after the detrimental quality of life aspects were taken into account, would result in the same number of quality-adjusted life years.[10]

Two models have been developed in the Australian context.[11,12] A recently reported decision model used a Markov process to simulate health outcomes and estimate the net benefit and cost of four-yearly lifetime PSA screening in men aged 50 versus no screening, as a function of the mens' underlying risk.[12] For Markov models, all transitions depend only on the current state of the individual and so the model usually has limited ability to reflect different risk profiles or management strategies according to screening or treatment history. Men were classified as being at average risk (baseline rates), high risk (double the baseline rates) and very high risk (five times the baseline risk). The disease natural history structure included both preclinical and clinical states, but did not explicitly model cancer stages (local, regional, distant) or differentiation grade (Gleason score). The cancer incidence rates used in this model were obtained from ERSPC and adjusted to Australian age-specific rates. Prostate cancer mortality was calibrated to ERSPC data, however age, stage, Gleason score and treatment-specific survival or harms

from short-term and long-term treatment effects were not explicitly modelled, nor was a distribution of testing uptake behaviours considered. The evaluation found that PSA screening was not cost-effective for men at an average-to-high risk of prostate cancer, but may be cost-effective for men at very high risk. Although this provides important initial information, one difficulty in interpreting the findings is that the opportunistic PSA testing that has been taking place in Australia over the last two decades was not taken into account in model development and its calibration to observed Australian prostate cancer incidence and mortality data. Given this, and that the results modelled a single cohort of 50 year-old men through life, caution should be used in applying the results to the whole population of men in Australia.

Another study has used a Markov model to compare annual PSA screening with no screening for men aged 40, 50, 60 and 70 years who are at low, medium or high risk for prostate cancer.[11] Risk was defined according to family history. The disease natural history structure included both preclinical and clinical states (localised and non-localised), but age, stage, Gleason score and treatment-specific survival and harms from short-term and long-term treatment effects were not explicitly modelled. The objective was to develop a model of annual PSA screening that could help individuals make informed decisions regarding PSA screening. The evaluation found that for 1000 men screened annually from 40 to 69 years of age, there will be 30 prostate cancer deaths and 640 deaths overall by age 85 years compared with 30 prostate cancer deaths and 640 deaths overall in unscreened men.

In summary, two comprehensive models of natural history have been developed internationally and two further models have been developed for Australia. However, none of these important evaluations have yet taken into account realistic levels of PSA testing uptake or the full range of strategies of interest in the Australian context. The Australian models, while providing important information, have not been designed as fully calibrated, individual-based flexible simulation platforms for prostate cancer, and have not been designed to be capable of simulating a wide range of PSA testing strategies and population-based outcomes in Australia.

Development of a comprehensive Australian model

The Cancer Screening Group at University of NSW, together with Cancer Council NSW, are currently developing an Australian model for the ongoing epidemiologic and economic evaluation of changes in the detection, management and treatment of prostate cancer, and of the interactive effects of these changes on outcomes (including cancer incidence, mortality and treatment-related morbidity) and costs. The model will be developed on the POLICY1 microsimulation platform, a flexible model for cancer screening applications, which has already been used to simulate cervical cancer and colorectal cancer prevention. The development of POLICY1-Prostate is being funded by the Prostate Cancer Foundation of Australia and will use Australian data to model current levels of PSA uptake and calibrate outcomes to current Australian data on prostate cancer incidence, mortality and morbidity rates. Evidence-

based quantifiable outcomes will be produced to support detailed recommendations for the optimal (most effective and most cost-effective) strategies for prostate cancer detection in Australia. The outcomes will include detailed predictions of prostate cancer incidence and mortality, effects on resource utilisation (such as the numbers of biopsies and specific prostate cancer treatments), and the cost-effectiveness and budget impact of a wide range of potential strategies.

POLICY1-Prostate will be readily usable for a range of future evaluations of new strategies for prostate cancer detection and management in Australia; these potentially include the role of specific testing strategies in men with a family history of prostate cancer, the role of new testing technologies, the effect of targeted efforts at testing men in low socio-economic groups and rural areas, future changes to diagnostic techniques or protocols, and the effects of changes in prostate cancer treatment patterns.

Conclusion

Investment in a carefully calibrated and validated disease model of prostate cancer development and PSA testing in Australia will provide an important platform for estimating the impact of various possible candidate strategies for PSA testing. The model, known as POLICY1-Prostate, will allow large scale simulations, at the level of the individual, of hundreds of thousands of men in the Australian population. This flexible tool will be designed to incorporate new data sources as they emerge and to evaluate new prostate cancer prevention strategies on an ongoing basis.

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