University of Sheffield

ScHARR

SCHOOL OF HEALTH AND RELATED RESEARCH

Option appraisal: screening for prostate cancer

Report to the UK National Screening Committee

May 2010

Version 2.0

Jim Chilcott

Silvia Hummel

Matthew Mildred

Executive summary

Aims and Objectives

The aim of the study was to develop a mathematical model to estimate the costs, benefits and resource implications of alternative screening options for prostate cancer in the UK. The impacts of four screening options using the prostate specific antigen (PSA) blood test conducted are assessed in comparison to no screening and to each other:

- a single screen at age 50 years,
- screening every four years from age 50 to 74 years,
- screening every two years from age 50 to 74 years,
- screening every year from age 50 to 74 years.

In addition a range of further screening options investigating the impact of screening at different ages and over different durations have also been examined.

Evidence on the effectiveness of screening for prostate cancer

The results of two randomised controlled trials (RCTs), one European[1] and the other from the US,[2] were published in 2009. The objective of both RCTs was to evaluate the effect of PSA screening on death rates from prostate cancer. They report conflicting results: the European Randomised Study of Screening for Prostate Cancer RCT (ERSPC[1]) showed a reduced death rate ratio in the screening group compared to the control of 0.8 (95% confidence interval 0.65-0.98) whereas the US Prostate, Lung, Colon, Ovary RCT (PLCO[2]) showed no statistically significant

difference in death rates between the screened and control group, although there were more prostate cancer deaths in the screened group compared to the control.

There is currently ongoing a large UK RCT of treatments for prostate cancer diagnosed by screening, the 'Prostate testing for cancer and Treatment' (ProtecT^3) trial. This UK RCT has a companion study comparing outcomes in a population with no organised screening (CAP). Results of these studies are expected to be available in around 2015.

Modelling the impact of prostate cancer screening

A systematic search and review of existing prostate cancer screening models was undertaken to identify alternative modelling methodologies and data sources and to inform the structure of the ScHARR prostate cancer screening model. Fourteen papers were identified for inclusion in the review, each of which employed a variety of modelling methodologies such as decisions trees, Markov-cycle trees, Monte Carlo Markov Chains, statistical mixture models and microsimulation. No UK screening models were identified in the original systematic review though a recent modelling paper has been published during the course of this work.

A patient level simulation model of prostate cancer screening has been built that allows the impact of screening policies on cancer diagnosis and subsequent management to be assessed. The model comprises prostate cancer natural history and epidemiology components with a model of screening management. The model is calibrated to available UK and European data regarding prostate cancer incidence and is validated against the BAUS Registry database.

A separate model is built that assesses the impact of changes in diagnosis on treatment, incremental resource use, costs, and harms to men through the adverse effects of diagnostic tests and treatment.

Results

Detection and staging of cancers

A one off screen at age 50 years is estimated to have minimal impact on longer term incidence of prostate cancer (PCa). However, more intensive policies can be effective in the early identification cancer, with four yearly and two yearly policies increasing the lifetime risk of PCa from around 10% under no screening to 16-17%. A small marginal increase in PCa identification is obtained by moving to an annual policy.

Overdetection has been defined as the detection of cancers in individuals who would otherwise have died of natural causes without a clinical diagnosis of PCa. All the repeat screening policies are estimated to entail over 45% overdetection of PCa. Overdetected cases are estimated to be exposed to an average of 11-13 years of management for their PCa.

Potentially relevant cancers are defined as screen detected cancers that would otherwise arise clinically at a later date. The estimated mean lead time for potentially relevant cancers is also approximately 11-13 years leading to a shift in stage of diagnosis, with 85% of locally advanced and 80% of metastatic cancers being screen detected at the local stage with a 4 year screening policy.

The repeat screen policies are associated with an expected life years gained of approximately 0.03 years (10-11 days) for each individual accepting screening, with an equivalent figure of 0.004 (1.2 days) for the single screen policy. Whilst screening policies can often be associated with small expected gains for each individual, prostate cancer screening is also associated with a high level of disease management, for instance for each life year gained the repeat screen policies are

associated with approximately 67-84 years of additional prostate cancer management and 36 years for the single screen policy.

The single screen at 50 policy is estimated to have a minimal impact on overall prostate cancer incidence and mortality rates, being the least effective policy in terms of relative rate of prostate cancer mortality, 0.96 as compared to 0.84 for the repeat screen policies.

Treatment

The analysis shows that screening once at age 50 (policy1) has little effect on current treatment patterns apart from a small rise in radical treatment following the screen. Radical treatment in the screened age groups increases with screening intensity. Assuming treatment patterns remain constant radical treatment would increase by 2.5 – 3 times for repeat screening policies, primarily in men aged less than 75 years. Repeat screening also increases the number of men treated with hormone therapy at some time in their life, but by a much lesser extent: by approximately 50% more relative to current activity.

Adverse effects of diagnosis and treatment

Adverse effects of the PSA test are rare and mild. Serious adverse effects of biopsy are infrequent, but nevertheless a small proportion of men (0.47%) will be hospitalized for infection resulting from biopsy. This will result in an additional 1500 men being affected for a four yearly screening policy.

The incidence of long term adverse effects of treatment increases with screening intensity. For example the additional number of men affected by urinary incontinence compared to no screening varies from 1400 for policy 2 and over 2000 for policy 4. Similarly there is up to an additional 1000 men suffering from long term bowel complications resulting from radiotherapy. By far the most common adverse effect of

treatment for prostate cancer is sexual dysfunction. Regular screening with a frequency of one to four years would increase the number of men affected by between 20,000 and 25,000, depending on policy. There is some uncertainty in these figures arising both from current treatment patterns (and also assumed future patterns), and dysfunction rates following treatment, but sensitivity analysis shows that even with more favourable assumptions at least 16,000 men would be affected with regular screening. Note the model has been careful not to overestimate the effects of PCa treatments on SD, by explicitly taking into account underlying SD in the male population, both in the incidence resulting from treatment, but also in the proportion of men that would have been affected in due course with increasing age. Screening policy also affects the age at which adverse events occur. If men are treated at a younger age for PCa as a result of screening they will also incur adverse effects earlier, and have to live with them longer.

QALYs (Quality adjusted life years)

QALYs allow differences in quality of life to be taken into consideration as well as differences in survival. All screening policies result in loss in QALYs: for repeat screening the loss ranges from 1.1 to 1.4 QALYs undiscounted, or 0.3 to 0.8 discounted QALYs, per man with prostate cancer (detected or not). The more frequent the screening, the greater the QALY loss. The loss in QALYs reflects the adverse effects of treatment. As sexual dysfunction is the most common adverse effect of PCa treatment its incidence, and the utility loss attached to it, are key parameters in determining incremental QALYs for different screening policies. Sensitivity analysis showed that QALYs remained negative for all of the baseline screening policies when varying these parameters.

Resources

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The resources most impacted are those required for screening itself. Policy 4 (annual screening) would result in almost 10 million more PSA tests per year and 1.4 million biopsies. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, hormone treatment, outpatient appointments) there would be some small savings in others relating to the diagnosis of more advanced disease such as bone and MRI scans.

Costs

The total additional lifetime discounted costs for a cohort of men aged 50 of a screen once policy at 50 are £50 million, rising to almost £1 billion for an annual screening policy. Note costs are discounted to age 50 for all policies and **do not include the costs of administering a screening programme.** The actual annual cost of screening is £0.6 to £1.7 billion per year. The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men screened falls. With an annual screening policy the costs of screening are greater than those for treatment. The proportion of the total cost comprised by each resource item varies slightly between policies. Biopsy costs in particular vary from 8% of the total cost for Policy 1 (single screen at 50) to 25% for Policy 4 (annual screening). For all policies outpatient attendances and hormone treatment are the two largest cost elements, varying between 30-35% and 19-36% of the total costs respectively.

Conclusions

A single screen at age 50 has little long term impact on overall age specific prostate cancer incidence and mortality rates.

Intensive annual screening has little marginal benefit over a policy of screening every two years.

Screening policies every two and four years are estimated to impact on early diagnosis and stage at diagnosis of prostate cancer. Cancers that would have been clinically diagnosed with background PSA testing at the level that was prevalent in 2004, would be diagnosed on average 11-13 years earlier.

The two and four year screening policies are associated with overdetection rates of over 45%, with excess management in the order of 12 years.

In order to obtain 1 additional year of life the modelling suggests that the repeat screening policies are associated with in the region of 60-90 years of additional prostate cancer management, with an equivalent figure of 35 years for the single screen policy. These results are reflected in the negative QALYs obtained for all screening policies, which suggest the harms of treatment outweigh the possible benefits of earlier disease detection.

Despite the impact on stage at diagnosis trials do not demonstrate any overall survival benefit from screening. The modelling suggests that any overall expected survival benefit is likely to be small, in the region of 1 day for per person being screened for the single screen at 50 policy and 10 days for the repeat screen policies. The uncertainty in these estimates would however be greater than their expected value. Though currently available trials necessarily reflect past treatment modes from an international setting, current UK information systems in prostate cancer describing treatment patterns and information on the effectiveness of those

treatments are insufficient to adequately adjust these international prostate cancer trial results for current UK survival.

The costs of implementing a screening policy are not inconsiderable: approximately £0.8 billion per year for a policy of four yearly screening between the ages of 50 to 74 years. The metric of incremental cost effectiveness ratio (ICER), commonly used in health economic analysis, is not applicable in these circumstances where the current situation of no screening is both less costly and more effective (more QALYs).

Table of contents

Acknowledgments

This study was commissioned by the UK National Screening Committee (NSC). We would like to acknowledge the input of the NSC committee members for providing guidance and support, in particular Dr Anne Mackie, Prof Julietta Patnick and the Scientific Reference Group to the Prostate Cancer Risk Management Programme. We would also like to thank Luke Hounsome and the rest of the Cancer Analysis Team at the South West Public Health Observatory (SWPHO) for providing national cancer registry data, and Sarah Fowler at the British Association of Urological Surgeons (BAUS) for also providing data. We would like to thank the ProtecT PIs - Freddie Hamdy, Jenny Donovan, David Neal; and the ProtecT trial co-ordinator, Athene Lane, and data manager Michael Davis - for making available the ProtecT study data.

Abbreviations

AM	active monitoring
3DCRT	3-dimensional conformal radiotherapy
BAUS	British Association of Urological Surgeons
BPH	benign prostate hyperplasia
CEA	cost-effectiveness analysis
DRE	digital rectal examination
ERSPC	European Randomised Study of Screening for Prostate Cancer
FHCRC	Fred Hutchinson Cancer Research Center
HT	hormone therapy
HRQoL	health related quality of life
IMRT	intensity modulated radiation therapy
LHRHa	luteinizing-hormone-releasing hormone analogue
LUTS	lower urinary tract symptoms
MISCAN	microsimulation for screening analysis
MRI	magnetic resonance imaging
NI	Northern Ireland
NICE	National Institute for Clinical Excellence
NSC	National Screening Committee
OCM	other cause mortality

ONS	Office for National Statistics
PCa	prostate cancer
PCOS	Prosate Cancer Outcome Study
PIVOT	Prostate cancer Intervention Versus Observation Trial
PLCO	Prostate, Lung, Colon, Ovary trial
ProtecT	Prostate testing for cancer and Treatment
PSA	prostate specific antigen
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life-year
QOL	quality of life
RCT	randomised controlled trial
RP	radical prostatectomy
RT	radiotherapy
SD	sexual dysfunction
SWPHO	South West Public Health Observatory
TNM	Tumour, Node, Metastasis staging of tumours:
	T – primary tumour; N – regional nodes; M – metastases
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
WW	watchful waiting

1.0 Aims and Objectives

The aim of the study is to develop a mathematical model to estimate the costs, benefits and resource implications of alternative screening options for prostate cancer in the UK. The impacts of four screening options using the prostate specific antigen (PSA) blood test conducted are assessed in comparison to no screening and to each other:

- a single screen at age 50 years,
- screening every four years from age 50 to 74 years,
- screening every two years from age 50 to 74 years,
- screening every year from age 50 to 74 years.

In addition a range of further screening options investigating the impact of screening at different ages and over different durations have also been examined.

2. Background

2.1 Prostate cancer

Prostate cancer is the most common cancer in men in the UK, excluding non-melanoma skin cancer.[4] Over 34,000 cases are diagnosed every year, accounting for over a quarter of all cancer cases diagnosed in men.[5] Prostate cancer is also the second most common cause of cancer death after lung cancer, with more than 10,200 mortalities.[6] The aim of screening is to detect disease in its early stages, before symptoms occur with the objective of improving treatment and survival rates. The potential benefit of screening is therefore to reduce disease specific mortality, and the morbidity and high costs associated with late-stage cancer and its treatment. There are several diagnostic tests/techniques to help inform patients and clinicians of the likely future progression of the disease, and thus the patient's suitability for receiving certain treatments; however many of the tests have a poor sensitivity and specificity. The PSA test is a diagnostic test which measures the level of prostate-specific antigen in the blood. Since its introduction in the 1980s there has been considerable discussion on the benefit of prostate cancer screening and the optimal design of a screening programme. Recently, the results of two large randomised controlled studies which evaluate the effect of PSA screening on prostate cancer death rates have also been published,[1;2] although the results were conflicting.

Whilst there has been an upward trend in prostate cancer incidence,[7] disease specific mortality rates have not significantly changed in the last ten years.[6] The disease is largely a disease of older men, with the average age at diagnosis between 70 and 74 years. The average age at prostate cancer caused death is 80-84, with 93% occurring in 65s and over. It is therefore commonly quoted that most men will die with prostate cancer – not of it.[8-10]

Due to the often slow-growing nature of the disease, the difficulty for clinicians is determining which men have fast-growing cancer, and therefore should receive treatment, and those for which the possible side-effects outweigh the benefits.

The following sections will outline the epidemiology of the prostate cancer, risk factors and possible causes of the disease. A brief introduction to screening methods and diagnostic techniques is also given, followed by an explanation of the classification and staging terminology used for the sake of completeness.

2.2 Epidemiology, risks & causes

The epidemiology of prostate cancer is an area of significant interest and widespread research, however the exact natural history and cause of the disease is still relatively unknown. Commonly accepted risk factors for prostate cancer include age, family history (genetic factors) and ethnicity. A number of other environmental factors such as life-style and socio-economic factors have also been suggested as contributing to an increased risk of prostate cancer.

The prostate is a small gland that resides in men below the bladder and in front of the rectum, which surrounds part of the urethra and is used in the production of semen. As men age the prostate gland often enlarges, a condition known as benign prostatic hyperplasia (BHP), which can cause urinary problems. However the presence of benign or malignant tumours can also have the same symptoms such as difficulty passing urine or pain. Although BHP often occurs in association with prostate cancer, it is not thought to be a precursor of the disease.

Whilst the majority of prostate cancers are very slow growing and do not pose a threat, a significant minority of cases progress rapidly. As the exact process of disease progression is not well understood, progression can broadly be described as the development of localised organ-confined cancer, before the invasion of

surrounding tissues, bones or other sites. Disease progression is however thought be related to the size and spread of the cancer and the loss of cell differentiation.

The risk of developing prostate cancer significantly increases with age. Approximately 80% of men will have cancer cells in their prostate by the age of 80.[9] It is also recognised that the relative risk of prostate cancer increase significantly with the total number of family members diagnosed. Ethnicity is widely accepted to be an important factor in the risk an individual has of developing prostate cancer. Black men are at a significantly higher risk of developing prostate cancer regardless of their country of origin.[11]

Factors that are less supported include life-style factors such as diet,[12] multi-vitamin intake,[13] sunlight exposure,[14;15] job-related chemical exposure,[16] smoking,[17] and level of physical activity.[18] It has also been suggested that socio-economic factors may influence the probability of developing prostate cancer or of being diagnosed with prostate cancer. This may be due to differences in the level of access to health services between social classes. Alternatively the level of education may play a part in that more educated people may be more informed and thus more likely to seek advice from a GP. Sexual activity and sexually transmitted infections have also been cited as possible risk factors.[19;20]

2.3 Screening methods and diagnostic tests

There are several diagnostic techniques available for determining the presence or extent of prostate cancer, with the three main procedures used to diagnose prostate cancer being digital rectal examination (DRE), PSA blood test, and transrectal ultrasound (TRUS) –guided biopsy; however the prevalence of such tests are not well recorded or centrally monitored.

Each of the diagnostic tests can be described in terms of accuracy and usefulness.[21] Both the ability to correctly discriminate between different health states and the

practical value of doing so can be expressed by means of sensitivity and specificity. Sensitivity is the proportion of subjects correctly identified with prostate cancer (i.e. a true positive), whereas specificity is the proportion of subjects correctly identified without prostate cancer (i.e. a true negative). An ideal (and therefore accurate) test would have a high sensitivity and a high specificity, though it is often seen as a trade-off between the two characteristics.[21] A useful test would therefore be sensitive and specific without unreasonable costs, or to put it another way, without being more expensive than another test with similar sensitivity and specificity. The ability to conduct the test (i.e. its complexity) is also a factor when considering the usefulness of a test, as is the level of patient discomfort or the invasiveness of the procedure.

2.4 Classification and staging of the disease

Prostate cancer is most commonly described by stage and grade, in addition to which tumour volume is sometimes also used. The tumour stage represents the size and spread of the cancer and there are various staging systems which classify and group tumours differently. The most common staging system is the TNM staging system, and is implemented within the NICE prostate cancer guidelines,[7] however the more general Jewett-Whitmore staging system is also used in the US.

The TNM staging system which stands for Tumour, Nodes, and Metastasis describes the anatomic extent of the primary tumour (T category), regional lymph nodes (N category), and distant metastasis (M category). The 24 detailed clinical stages and 8 pathologic stages of the TNM system is also frequently regrouped into four broader clinical stages as shown in Table 1 (see Appendix A for full descriptions of both staging systems).

The clinical stage is based on information prior to surgery, and the pathologic stage is based on information post surgery when the whole tumour can be examined.

Table 1. Comparison of TNM and Gleason score combined groups with corresponding clinical stage.

Clinical Stage	TNM		Gleason score
Stage I:	T1a/N0/M0	&	(Gleason score 2-4)
Stage II:	T1a-T2/N0/M0	&	(Gleason score 5-10)
Stage III:	T3/N0/M0	&	(Any Gleason score)
Stage IV:	T4/N0/M0	&	(Any Gleason score)
Or	any T given N1 or M1	&	(Any Gleason score)

The histological grade of the tumour, denoted by its Gleason score, is an assessment of cell differentiation, thought to be measure of aggressiveness. Following prostate biopsy, a sample of tissue is examined under a microscope in order to determine the level of cell differentiation; to which a score is given accordingly. The overall Gleason score comprises the score of the two most frequent patterns of cell differentiation; 1 being well differentiation (good prognosis) and 5 being poorly differentiated (poor prognosis). The overall Gleason score can therefore vary from 2 to 10. Men with higher scores (Gleason score7-10) are thought to be at higher risk of disease progression. To complicated matters, ranges of Gleason score are often referred to by specific terms (see Table 2) or by histological grade (denoted by a capitalised G).

Table 2. Common classifications of Gleason score.

Histological grade	**Gleason score**	**Description**	
GX	-	Cannot be assessed/Unknown	
G1	2-4	Low grade	Well differentiated
G2	5-6		
G3	7	Intermediate grade	Moderately differentiated
G3	8-10	High grade	Poorly differentiated

3. Effectiveness of screening for prostate cancer

Since the introduction of the PSA (Prostate Specific Antigen) test in the 1980s there has been a debate as to whether older men should be routinely screened for prostate cancer. Although prostate cancer is a significant cause of death (10,000 deaths in the UK, 2006[1]), the case for screening is not clear cut, for the reasons outlined below.

The test itself has poor specificity. Increased PSA levels are associated with a raised probability of prostate cancer, but many men with raised levels do not in fact have prostate cancer. In a screening trial 76% of men with raised PSA levels had a false positive result.[1]

To make a diagnosis of prostate cancer a biopsy is required which risks minor complications such as discomfort and bleeding.[22] There is also a small but serious risk of infection, the magnitude of which varies according to the number of biopsy cores taken and antibiotic prophylaxis.[22] In the ERSPC trial which used sextant biopsies and antibiotic prophylaxis prior to and post–biopsy 3.5% of men developed fever, and 0.5% required hospitalization and intravenous antibiotic therapy.[23]

Men diagnosed with cancer then have a difficult decision as to what treatment to choose. Most screen detected cancers are low stage (confined to the prostate) and low grade, (indicating more indolent disease progression), and may never cause clinical symptoms in the man's lifetime. Autopsy series show prostate cancer prevalence in men aged 50 years and over to be greater than 50%, but lifetime risk of death is 3%.(Pomerantz, 2008) There is however considerable uncertainty in distinguishing indolent from aggressive cancers.[24] Active monitoring is an option for some men, avoiding immediate radical therapy. Research is ongoing as to the optimum monitoring regimes and the criteria used to reconsider the need for radical therapy.[25;26] Adverse effects of radical treatment such as sexual dysfunction and urinary incontinence are common, and may be enduring.[27-29]

3.1 Trial Evidence

Two large screening trials, one European, the other from the United States with several years follow up presented their results last year.[1;2] Both had the objective of evaluating the effect of PSA screening on death rates from prostate cancer. The results, however, do not provide a clear answer as to the benefit of PSA screening or otherwise. Firstly, the two trials report apparently conflicting results. The European study[1] (ERSPC) showed a reduced death rate ratio in the screening group compared to the control of 0.8 (95% confidence interval 0.65-0.98). The US study[2] (PLCO) showed no statistically significant difference in death rates between the screened and control group, but there were more prostate cancer deaths in the screened group compared to the control. Reasons for the difference in results will be examined in more detail below. The second issue is that, even if the results of the European study are considered more representative of the likely mortality benefit the UK, the balance of benefits is not clear cut. In order to prevent one death from prostate cancer 196 men will have a prostate biopsy and 48 men will be treated for prostate cancer, some of whom will suffer lifetime morbidity resulting from treatment.[1]

In order to try and explain why the two trials reported different findings, key characteristics of the trial population, study design and environmental factors were examined. Variables such as age distribution of the screened and control groups, population size, screening intervention used, screening compliance and contamination rates and the underlying level of screening prior to trial enrolment were examined.

The age distribution of the screened and control arms for the ERSPC study is not reported, although the average age across the seven European countries can be calculated as 61.2 and 61.3 years respectively. In comparison to the PLCO study, where the quintile age distribution is reported, the US population is marginally older

at 62.9 years for both arms. This difference may have contributed to the higher overall incidence observed in the PLCO study.

The population size of the ERSPC is more than double that of the PLCO trial, thereby increasing the power of the study. When examining the contamination rates of the two studies, this factor becomes an important consideration, and strengthens the weight of Schroder *et al.*'s[1] conclusion.

The level of contamination, that is the number of subjects from the control group undergoing some form of intervention that is being administered in the screened group, was high in the PLCO study; rising from 40% in the first year to 52% in the sixth year.[2] Whilst contamination was not routinely measured in the ERSPC, it was estimated to be 20%.[1] The level of contamination is significant in that a high level of contamination reduces the ability to make insightful inferences between the control and the screened arms. Contamination may therefore result in an underestimate of the benefits of screening.

The screening interventions differed significantly between and within both the ERSPC and PLCO trials there by making it difficult to compare and assess the effectiveness of the PSA test on reducing disease specific mortality. A DRE was given in the first four years of the PLCO trial along with the PSA test, before it was removed from the screening procedure for the remaining two years. The threshold for a positive PSA test in the PLCO trial remained fixed at 4 ng/ml, whereas the PSA threshold among the European countries varied. The majority of test in the ERSPC study used a PSA threshold of 3 ng/ml. Finland, which comprised almost 50% of the European trial population, used the same PSA threshold as in the PLCO trial. For a period of time in Belgium a PSA cut off value of 10 ng/ml was used. To further complicate the matter, various ancillary tests with different criteria for their use were used in Finland, Italy, the Netherlands and Belgium.

An important factor that may explain the difference in the trials findings is the degree to which subjects received screening for prostate cancer prior to entering the study. A significant amount of uncertainly surrounds such a comparison, as the extent of prior screening was not routinely measured in the ERSPC trial, although it has been estimated to be between 7% in 1996 rising to 14% in 1999 in Finland which comprised almost half of the European study population. In comparison to the PLCO trial, 44% of subject had previously had a PSA test, and over 50% having previously received a DRE. With such a large proportion of the US population exposed to some form of prior screening, it is difficult to make a proper assessment of the screening intervention, as the trial is effectively comparing a certain level of screening with a higher level of screening.

Partial information on the cancer stage of the ERSPC and PLCO studies was reported. The ERSPC study reported cancer in terms of TNM stages, where T is the primary tumour, N is regional lymph node involvement and M is distant metastasis. The PLCO on the other hand reported cancer in terms of the more general Clinical stage.

In order to compare stage distribution of the ERSPC and PLCO, two assumptions had to be made: Missing/unknown data was assumed to have a similar stage distribution as known subjects, and where nodal status was unknown, N0 (no lymph node involvement) was assumed. This analysis showed that there appeared to be a positive stage shift in the size, spread and aggressiveness of cancers in the ERSPC from the control to the screened arm. This may therefore lead to the conclusion that the reduction in death rate ratio between the screened and the control arms in the ERSPC is due to the intervention.

In a recent investigation into contamination and non-attendance within the ERSPC, Roobol *et al.*[30] adjusted for these factors and found that relative prostate cancer mortality reduced by approximately half to 31-33% for those than underwent screening. Whilst Roobol *et al.*[30] only used data from the Rotterdam section of the ERSPC and extrapolated the data to the whole study, the finding further support the benefits of screening.

van Leeuwen *et al.*[31] take a different approach to the analysis of contamination within the ERPSC. Acting as the control, a sample of the male population of Northern Ireland (NI) is compared with the screened arm from the Rotterdam section. Both populations consisted of predominantly white men and median age at study entry was 63 years ($p = 0.184$), however the age distribution was significantly different.[31] Also, men with any other prior diagnosis of cancer, except non-melanoma skin cancer, were excluded from the control.

The NI population was used as the control arm because it had a low intensity of screening. van Leeuwen *et al.*[31] report that reduction in relative prostate cancer mortality is even greater at 37%. However there are several factors that may have contributed to this result. The control was still subject to contamination and median age at diagnosis was also significantly different; 70 verses 67 years ($p < 0.001$). This age difference may contribute to the findings in two ways. Firstly the older men of the control group were more likely to die of other causes thereby decreasing disease-specific mortality rates. Secondly, treatments may be more effective in the younger screened group, therefore improving prostate cancer mortality rates.

Roemeling *et al.*[32] use multivariate regression to investigate the relationship between initial PSA level, Gleason score and number of biopsy cores with prostate cancer at screening and development of metastases within the Rotterdam section of the ERSPC. Roemeling *et al.*[32] report that the aforementioned attributes are indeed

independent predictors for the development of metastases, however the number of positive biopsy cores lost its predictive values after 60 months of follow-up. The high prevalence of metastatic-free survival within the Rotterdam section however may be a result of a downgrading of cancer and particularly overdiagnosis which is associated with large screening programmes.

4. Review of existing prostate cancer screening models

4.1 Introduction

This chapter presents a review of existing prostate cancer screening models and the methodologies employed within them. The review was conducted in order to identify if any of the health economic models of prostate cancer screening could be applied to the UK situation or aid in model development. The validity and relevance of the models are therefore evaluated in terms of modelling approach, structural assumptions, method of model calibration and the robustness of the results. Particular attention is given to the handling of the disease natural history as this is a key factor within a sound screening model.

4.2 Search strategy

A systematic search was conducted in Medline, the largest specialist medical literature database, and cross-referenced with lists of relevant articles from various health services research resources; such as HTA organisations and guideline producing bodies. The aim of the literature search was to identify both theoretical and applied models of the natural history of prostate cancer. A literature search strategy was therefore devised and subsequently refined in an iterative process in order to be both comprehensive and yet specific (see Appendix B for full strategy). Given the relatively new introduction of the PSA blood test as a screening tool, the search was carried out from 1994 so as to return only the most up-to-date and relevant papers. Each of the search terms entered were medical subject headings (MeSH), which are keywords from the US National Library of Medicine's controlled vocabulary thesaurus. The MeSH library contains sets of "naming descriptors in a hierarchical structure that permit searching at various levels of specificity.[33] For instance the

MeSH term ‘Prostatic Neoplasms’ includes 18 synonymic keywords relating to prostate cancer. The search strategy was formulated following expert advice on the subject of conducting systematic reviews from information specialists at ScHARR.

An extensive list of model types was created including specific modelling techniques returned from the early versions of the literature search such as proportional hazard models or those using the Monte Carlo method. Whilst the search was designed to be as broad as possible in terms of modelling approaches, at the risk of excluding potentially relevant and applicable non-prostate cancer related models, the search was restricted to only those models pertaining to prostate cancer screening. This was done so as to focus the search on the handling of the complex disease natural history specific to prostate cancer. After hand searching over 1000 potentially relevant economic studies returned by the search, fourteen studies were identified for full review.

4.3 Inclusion & Exclusion Criteria

General inclusion and exclusion criteria were defined in order to specify which papers should be included within the full literature review. Studies which compared or tried to improve prostate cancer screening strategies, whether it be in terms of detection rates, a reduction in late stage incidence, mortality, lead-time, over-detection, risks, benefits or costs were included. Studies which evaluated prostate cancer screening with or without considering treatment were also reviewed. Papers which were concerned with groups of men with specific underlying health conditions were excluded, as were animal related studies. Studies reported in languages other than English were not included.

4.4 Studies indentified for inclusion within the review

The following section will outline the research question, model structure and modelling techniques of these papers, and will present them by group of authors or

lead-author. Within the papers a number of different mathematical and simulation modelling techniques have been applied, ranging from relatively simple decision trees and cohort Markov models, to more complex population and individual sampling models that override the Markovian (no memory) assumption of exponential transition rates between health states.

4.5 Prostate cancer screening model structures and assumptions

There is considerable variation among the reviewed studies with regard to the modelling of the underlying disease natural history. Additionally the number of major assumptions made within the model and the justification behind them varies significantly. The following section will therefore highlight and discus key features of the models starting with relatively simple modelling techniques such as decision trees, and progressing on to more complex microsimulation models (as depicted in Table 3 below). The process of reviewing the models, combined with the availability of data and information around treatment and current practice was central to the model development.

Table 3. Modelling techniques of the papers identified by the literature search.

Author(s)	Modelling technique	Cohort/Patient
Perez-Niddam *et al.*[34]	Decision tree	Cohort
Holmberg *et al.*[35]	Decision tree	Cohort
Kobayashi *et al.*[36]	Markov-cycle tree	Cohort
Krahn *et al.*[37]	Markov	Cohort
Coley *et al.*[38]	Markov	Cohort
Ross *et al.*[39;40]	Monte Carlo Markov Chain	Patient
Tsodikov *et al.*[41;42]	Statistical mixture model	Cohort
Etzioni *et al.*[43-46]	Markov microsimulation	Patient
Draisma *et al.*[47-50]	Markov microsimulation	Patient

4.6 Review and discussion of existing model structures

4.6.1 Perez-Niddam et al.[34]

Perez-Niddam *et al.*[34] construct separate decision trees to evaluate two prostate cancer screening strategies for the 50 to 70 year old male population of France. The two strategies consist of a PSA test followed by a DRE, or vice versa, and are evaluated in terms of cost-effectiveness and the number of cancers detected.

Perez-Niddam *et al.*[34] argue that in the absence of strong evidence for the effectiveness of treatment, including it in their model would be unjustified. This therefore means that QALYs cannot be calculated, and instead the cost-effectiveness ratio per potentially treatable screened cancer is used.

Following the initial two screening tests, it is assumed that transrectal ultrasound guided needle biopsy (TUNB) is required if PSA is high (> 4 ng/ml) or DRE is abnormal; however if the two examinations are normal, no further diagnostic tests are needed other than rescreening at a later date. If the TUNB is positive, staging tests such as a pelvic CT, bone scan or lung x-ray take place, otherwise monitoring in the form of a repeat PSA test occurs.

As the decision tree does not feature treatment or QALYs, an alternative to incremental cost-effectiveness rations (ICERs) had to be devised. The potential cost of the screening/diagnostic strategy divided by the number of stage A or B prostate cancers (tumours limited to the prostate capsule classified using the Whitmore-Jewett staging system) was therefore calculated in order to give a cost-effectiveness ratio. As the screening and diagnostic tests being compared have few side-effects, this method may therefore be the most suitable means of cost comparison between the strategies. Ultimately however, the model is of limited use as the treatment, survival and health related quality of life is not incorporated.

4.6.2 Holmberg et al.[35]

Holmberg *et al.*[35] also use decision trees to evaluate the public health implications and cost-effectiveness of screening versus no screening for the Swedish male population. The model is based on a limited RCT, referred to as the Norrköping trail,[51] which began in 1987. A cohort of men aged 50-69 were invited to undergo screening every three years for a total of four occasions. A decision tree for each of the screening occasions was therefore constructed with a branch for the screened arm, and a branch for the unscreened control group. Screening consisted of DRE examination for the first two occasions, before it was changed to PSA testing for the remaining six years. During the whole study fine-needle aspiration biopsy was performed after abnormal DRE results or PSA > 4 ng/ml. Detected prostate cancer was then categorised as localised or advanced, and subsequent treatment (based on a medical record study[52]) given accordingly. Primary treatment for localised cancer was either expectant management or curative treatment, whereas it was expectant management or palliative treatment for advanced cancer. The paper however does not give any information as to the definition of what localised or advanced cancer is. Additionally no further information is given on the specifics of the primary treatments. Mean accumulated costs for treatments, estimated from the medical record study,[52] is given and the screening strategies are evaluated in terms of incremental cost per detected cancer and cost per curative treated cancer.

Whilst the screening and overall primary treatment costs are reported, numerous procedural costs relating to the management of prostate cancer are given although the relationship between these costs and the overall primary treatment cost is not reported. Examples of procedures costed include that of a GP visit, a urine culture, a six session course of palliative radiation therapy, hospital or nursing home inpatient care and even the cost of a urologist telephone call per minute.

In comparison to the Perez-Niddam *et al.*[34] decision tree, this model may be considered superior in that treatment costs are included, however it still falls down at the same place as health related quality of life and treatment related morbidity and adverse-effects are not modelled.

4.6.3 Kobayashi et al.[36]

Kobayashi *et al.*[36] use a Markov-cycle tree to determine if personalised PSA-specific rescreening intervals are incrementally cost-effective. Five screening strategies were evaluated for both annual and biennial PSA testing intervals. A different strategy was designed for men with baseline PSA levels of ≤ 1.0, ≤ 2.0, ≤ 3.0, ≤ 4.0 and > 4.0 ng/ml. Screening did not include DRE or TRUS, however for men with a PSA > 4.0 ng/ml TRUS guided biopsy was recommended. Men with positive PSA results but a negative biopsy result transitioned to PSA > 4.0 ng/ml. Detected cancers were categorised clinically into organ-confined disease (OCD), extracapsular but non-metastatic disease (ECD) and metastatic disease (MD).[36]

Whilst the model includes an overall cost of treatment for OCD, ECD and MD, no detail is given as to the exact nature of these treatments. Additionally the author implies that indirect-costs were not included. Quality of life (QOL) utilities obtained from Krahn *et al.*[37] and Kattan *et al.*[53] for curable, metastatic and recurrent disease are used to calculated QALYs and the ICERs, however the QOL impact of participating in the screening program is not included. This simplification may therefore contribute to an overestimation of the benefit of screening.

Costs and outcomes are both discounted at a rate of 3% so that costs incurred in the future are effectively less costly than those incurred in the present. Reporting of parameters and results of the study is good and sensitivity analysis is conducted for all main parameters including three scenarios (low, intermediate and high) for the probability of developing cancer.

4.6.4 Krahn et al.[37]

Krahn *et al.*[37] use a Markov model to model long-term prognosis for a cohort of men under four different screening strategies from a combination of DRE, PSA and TRUS, in order to determine the clinical and economic effects of screening (see Table 4 for details of screening strategies). The screening strategies are evaluated in terms of QALY gain and cost-utility ratios. The four stages of the Jewett-Whitmore staging system (Stages A, B, C and D) comprise the health states within the model, and it is inferred that cycle length is one year.

Table 4. Screening strategies investigated by Krahn *et al.*[37]

No.	Screening strategy
1.	DRE (followed by ultrasound-guided biopsy for a palpable nodule or induration)
2.	PSA (followed by confirmatory DRE and TRUS if PSA level above specified threshold)
3.	DRE and PSA (followed by TRUS and biopsy if PSA level above specified threshold)
4.	DRE, PSA and TRUS (followed by biopsy if any single abnormal result)

Krahn *et al.*[37] make a number of assumptions regarding treatment of subjects in each health state. For instance, Clinical Stage A and B were treated by radical prostatectomy, with Clinical stage C treated with external beam radiotherapy, and Clinical stage D treated by orchiectomy. Additionally it is assumed that subjects with incurable but treatable Stage C and D disease detected at screening would clinically present within the same year had the disease not been detected. This therefore means that the benefit of screening is limited to curable Stage A and B disease.[37]

One of the main limitations of this model, is that each of the strategies consist of just one screening round – as opposed to a series of repeated screens. Whilst this simplification may aid model implementation, it is not as insightful as a series of repeated screens that may be more likely to take place in the real world.

Krahn *et al.*[37] calculate utilities for chronic health states using the time-trade-off method. A group of ten experts including urologists, radiation oncologists and internists determined the number of remaining life years they would exchange in order to remain in a particular health state. A utility for a particular health state is therefore calculated by dividing the number of "healthy years" by the remaining life expectancy. A utility of zero therefore corresponds to the value of being dead, whilst a utility of one is the value of living in perfect health. Whilst it methodologically speaking, it is good to incorporate utilities, the validity of the utilities used is questionable when you consider that metastatic disease is given almost the same utility as complete incontinence (0.58 compared to 0.61 respectively).

Krahn *et al.*[37] also use survival data of clinically diagnosed patients to inform the model of survival for screen detected subjects. Caution should be taken when selecting an appropriate source of data as the stage and aggressiveness of symptomatic cancer may not necessarily be the same as asymptomatic cancer, and thus the natural history may not be equivalent.

4.6.5 Coley et al.[38]

Coley *et al.*[38] use a decision analytic model, based on the treatment model of Fleming *et al.*[54] to evaluate the benefit and economic outcomes of a onetime DRE and PSA test screening strategy for a cohort of men aged 50-79. As previously mentioned in the case of Krahn *et al.*'s model,[37] evaluating a one off screening strategy without considering serial screening rounds may have little real world application and as such may be considered a limitation of the study.

Regarding the previously mentioned Markov model of Fleming *et al.*,[54] whilst it was returned in the literature search, its application to the analysis of treatment strategies rather than screening meant that it was disqualified for full review by the exclusion criteria. Seeing as detail of the semi-Markov process used by Coley *et al.*[38] is scarce however, information regarding the Markov process were obtained directly from

Fleming *et al.*[54] Following radical prostatectomy, external-beam radiation therapy or watchful waiting, survivors enter a five-state semi-Markov process comprising:

- no evidence of metastatic prostate cancer
- metastatic cancer which can be suitably treated with hormone therapy
- metastatic cancer that cannot be suitably treated by hormone therapy
- death from metastatic prostate cancer
- death from other causes

Cycle length is set to 6 month intervals, during which the subject may die from other causes, develop bladder outlet obstruction requiring corrective surgery, remain in the same state or progress to one other aforementioned health states. The relative performance of each therapy is then evaluated using the quality-adjusted life expectancy of each therapy.

The model assumes that no cancer will be detected in 85% of the screened population, with the remaining detected cancers classified as tumour < 0.5ml in volume; intracapsular tumour > 0.5ml; and extracapsular tumour > 0.5ml. Regarding treatment, it is assumed that localised prostate cancer will be treated by radical prostatectomy, and that disease confined to the prostate capsule would be cured by the treatment. Extracapsular disease would therefore not be cured, and in fact survival rates would remain the same as those who did not receive treatment.

One particular feature that discriminates the work of Coley *et al.*[38] from the other models is that cancer-specific mortality rates are determined by the grade rather than stage of the tumour for clinically localised cancers. For instance, well differentiated tumours have the same prognosis for intracapsular disease as they do for extracapsular disease. However it is somewhat unintuitive to assume that cancer that has not spread as far throughout the body would have the same risk of mortality.

4.6.6 Ross et al.[39;40]

Ross *et al.*[39;40] use Monte Carlo simulation within a four state Markov model to compare prostate cancer mortality, PSA testing rates and biopsy rates; using seven screening strategies (as described in Table 5). Screening strategies are evaluated by the incremental cost-effectiveness ratio. Men are classified by and progressed through 6 states: (1) disease free; (2) organ-confined prostate cancer volume ≤ 0.5ml; (3) organ-confined prostate cancer volume > 0.5 ml; and (4) non–organ confined prostate cancer (metastatic); before terminating in (5) mortality due to prostate cancer; or (6) mortality not due to prostate cancer. Cycle length is set to 1 year, and men can either stay in the same state, progress to the next state or die from other causes.

Table 5. Screening strategies used by Ross *et al.*[39;40] in their Markov model

Age	Screening interval	PSA threshold	Screening strategy
-	-	-	A (No screening)
40-75	5 years	4.0 ng/ml	B
50-75	2 years	4.0 ng/ml	C
50-75	1 year	Age-specific *	D
50-75	1 year	4.0 ng/ml	E (Standard)
50-75	1 year	2.5 ng/ml	F
50-75 (with 40 & 50)	2 years	4.0 ng/ml	G
50-75 (with 40 & 50)	1 year	4.0 ng/ml	H

* 50-59: 3.5 ng/ml
60-69: 4.5 ng/ml
70-75: 6.5 ng/ml

The model used cancer state specific biopsy detection probabilities that are assumed to increase with cancer stage. Whilst the base-case model also made numerous major assumptions regarding treatment effectiveness, the Monte Carlo simulation

sought to investigate the sensitivity of the parameters values. In the base-case, treatment was assumed to be 100% effective for men with organ-confined prostate cancer volume ≤ 0.5ml, as they were considered cured by surgery, whereas men with organ-confined prostate cancer volume > 0.5ml had a 90% probability of being cured by surgery. Surgery caused mortality was assumed to be 0.5%. Within the sensitivity analysis however, treatment efficacy remains high for intracapsular and extracapsular disease (at 90% and between 80-100% respectively). This assumption would therefore favour frequent screening compared to less frequent screening or no screening.

Ross *et al.*[39;40] assumes that all men are treated for prostate cancer surgically even though this is completely unrealistic. Health related quality of life is also not modelled; instead person-years of life saved discounted at 3% per annum is used. This is another significant limitation with the model as it does not take into account adverse-effects associated with radical prostatectomy such incontinence or sexual dysfunction. As previously mentioned, adverse-effects of treatment should not be overlooked, as the side-effects may have a significant impact on quality of life.

4.6.7 Tsodikov et al.[41;42]

Tsodikov *et al.*[41;42] use a statistical mixture model to estimate age specific lead time, overdiagnosis rates and mortality, in the absence and presence of yearly PSA screening for men over 50. The purpose of the model was to analyse the relationships between PSA dissemination and trends in prostate cancer incidence and mortality, in order to inform policy decision making regarding PSA screening. The natural history is modelled by the progress through three consecutive stages: disease-free, pre-clinical and clinical. It is assumed that transitions are irreversible; meaning that once a person has progressed from the disease-free or pre-clinical stages they cannot go back. Prostate cancer incidence before the age of 50 is set to

zero because it is considered to be 'negligibly small',[41] and PSA tests performed with 3 months of diagnosis were considered as diagnostic.

A number of trend functions are used within the model to incorporate the grouped effect of several unspecified factors. For instance, environmental factors that may affect disease progression such as diet, exercise or lifestyle choice are modelled using a trend function. Improvements in detection technology, or other factors that may affect the pattern of disease onset, are also thought of as part of the trend function. A similar hazard function is used to model changes in the practice of cancer detection, and variation in cancer awareness, which may contribute to increased incidence.

4.6.8 Etzioni et al.[43-46]

Etzioni *et al.*[43-46] first created a microsimulation called PCSIM[43;45] based on the a Markov disease progression model of Cowen *et al.*,[55] before it was further developed and took the name PSAPC.[44;46] The objective of PCSIM was to compare screening options in terms of the expected number of life years saved, with and without screening, for five different screening strategies; treatment however is not modelled. The objective of PSAPC however was to investigate the relationship between PSA screening and the decline in prostate cancer mortality and shift in distance stage incidence. This review will therefore focus on the earlier works of Etzioni *et al.*[43;45]

The five screening strategies were defined by the frequency of screening and the PSA thresholds; above which biopsy is conducted. The screening intervals and PSA thresholds for the five screening strategies are therefore:

Annual and biannual screening with biopsy if PSA > 4.0 ng/ml; annual and biannual screening with age specific PSA threshold as proposed by Oesterling *et al.;*[56] and finally screening every 5 years with biopsy if PSA > 4.0 ng/ml.

The disease progression Markov model incorporated within both PCSIM[43;45] and PSAPC[44;46] models uses the pathologic stages of the Jewett-Whitmore staging system as states, rather than the more specific TNM staging system.

The model first determines which individuals will have histological cancer and their age, with disease progressions occurring according to age-specific transition rates. The clinical presentation component determines which subjects would have presented, and thus been diagnosed with prostate cancer, had screening not taken place.

Etzioni *et al.*[43-46] use data from the US National Cancer Institute's Surveillance Epidemiology and End Results program (SEER)[57] to inform their model on the level of disease incidence. Linear interpolation is used to extrapolate SEER incidence data from 1973-1987 for before and after. It is assumed that the stage-specific disease incidence prior to 1973 was the same rate as between 1973 and 1975. Additionally it is assumed that the stage-specific disease incidence after 1987 was the same rate as between 1985 and 1987. Such assumptions on the rate of incidence and the use of linear interpolation may be too simplistic.

Etzioni *et al.*[43-46] use Oesterling *et al.'s* annual PSA growth rate of 3.2% for men without prostate cancer was used plus a small random error (mean 0, s.d. 0.05).[56] Different annual PSA growth rates for men with metastatic or non-metastatic disease were based on Inoue's results.[58] Latent PSA growth rates are approximately half the rate of local-regional cases. Rates of onset for stage A1 prostate cancer, segregated by five-year age intervals from the age of 30 years onwards, are derived from SEER data.

Etzioni *et al.*[43-46] obtain age specific death rates of other cause mortality from US life tables.[59] In the absence of screening, death rates follow those from the pre-PSA era in SEER. This method may be a suitable way of determining death rates without the

influence of PSA testing, though may other factors such as public awareness of prostate cancer may have changed since the pre-PSA era, and thus contribute to a significantly different death rate to the present.

4.6.9 Draisma et al.[47-50]

Four papers by Draisma *et al.*[47-50] using a semi-Markov model known as the MISCAN (microsimulation for screening analysis) model were identified. MISCAN models have been applied to many problems relating to cancer screening including colon,[60] breast[61] and cervical cancer.[62] The prostate cancer screening models returned by the literature search investigate issues such as lead-time and over-diagnosis, [47;49;50] and the relationship between cell differentiation (Gleason score) and the use of PSA screening.[48]

Nine different screening strategies were evaluated for a cohort of men aged 55-75 years, namely a single test at 55, 60, 65, 70, or 75; annual screening from 55-67 or 55-75; and screening at 4 year intervals from 55-67 or 55-75. Individual life histories are described through a Markov process of states and transitions. Within the model there are six events relating to the development of prostate cancer, namely: (1) Tumour initiation; (2) Cancer becomes detectable by a screening test; (3) Clinical diagnosis or (4) Detection by screening; and finally (5) Cancer-specific death or (6) Death from other causes. It is assumed that death from other causes occurs independently to the development of cancer. The model has nine different preclinical states with individual transition probabilities and dwelling-time distributions with stage- and grade- dependent mean and shape parameters. The nine preclinical states are the product of three cancer stages (localised, regional and distant) and three differentiation grades, namely well, moderately and poorly differentiated (Gleason score <7, 7 and >7 respectively). Transition probabilities between the health states are estimated by “minimising the difference between the observed and the predicted number of cancers”.[50]

Three variations of the basic MISCAN model are also developed by Draisma *et al.* (2003)[50] to consider:

- Latent localised stage cancers (cancer with a very slow rate of development).
- The duration of preclinical cancer stages following exponential distributions rather than Weibull distributions.
- The effect of fixing Gleason score once a tumour has become detectable by screening.

Draisma *et al.*[47-50] fitted their MISCAN models to results of the Rotterdam section of the ERSPC[1] study. Data from the Netherland National Cancer Registry is used to obtain age-specific incidence of prostate cancer for the pre-PSA eta.

4.7 Summary of existing economic evaluations

The review of existing prostate cancer screening models highlights numerous methodological approaches to modelling the natural history, screening and treatment processes that interact with one another. Whilst more complicated structures facilitate the ability to represented the detailed interactions between these components, many more assumptions have to be made. The natural history component of the model be should sufficiently detailed to allow adequate modelling of the major clinical groups and their associated treatments, from which health related quality of life can be calculated. However due to the implicit unobservable nature of asymptomatic prostate cancer and the lack of data to calibrate to, the disease process is often significantly simplified. Additionally the lack of high quality data and evidence of treatment effectiveness means that treatment and follow-up is often omitted.

As seen within the reviewed models, the complexity of the natural history process can be thought of on a spectrum from the relatively simple decision trees of Perez-Niddam *et al.*[34] and Holmberg *et al.*[35] to more complex multi-state Markov models of

Draisma *et al.*[47-50] Given the relationship between sophisticated models and the extent to which model parameters must be calibrated to observed data, the reviewed models were subject to one or more of the following limitations:

- Oversimplification of the underlying disease process.
- Assumptions of perfect compliance thus overestimating the effectiveness of a screening programme.
- The absence of treatment or the assumptions of perfect treatment efficacy which therefore overestimates the benefit of screening.
- Failure to include quality of life effects associated with diagnosis and subsequent treatment.
- Oversimplification of the screening process and an absence of alternative screening strategies to contrast.
- Poor reporting of the calibration process of fitting unobservable input parameters to published data.

The application of more suitable structural model assumptions and the identification of better quality evidence may have avoided some of these limitations. However due to the scarcity of current evidence/data, key uncertainties around the disease natural history and treatment effectiveness may not be resolved.

5. The ScHARR prostate cancer screening model

5.1 Overview

A patient level simulation model of prostate cancer screening has been built that allows the impact of different screening policies on cancer diagnosis and subsequent survival to be assessed. The model comprises of prostate cancer natural history and epidemiology components together with a model of screening management. The model is calibrated to available UK and European data regarding prostate cancer incidence and screening and is validated against the BAUS Registry database. The screening model was implemented in the discrete event simulation package Simul8 (Version 15.0).[63]

5.2 Model structure

The structure of the prostate cancer natural history model is given in Figure 1. The model allows incidence of preclinical cancers that progress through a set of sequential disease stages; Gleason scores are tracked through the model as characteristics of the individual. The definition of the disease states is given in Table 6.

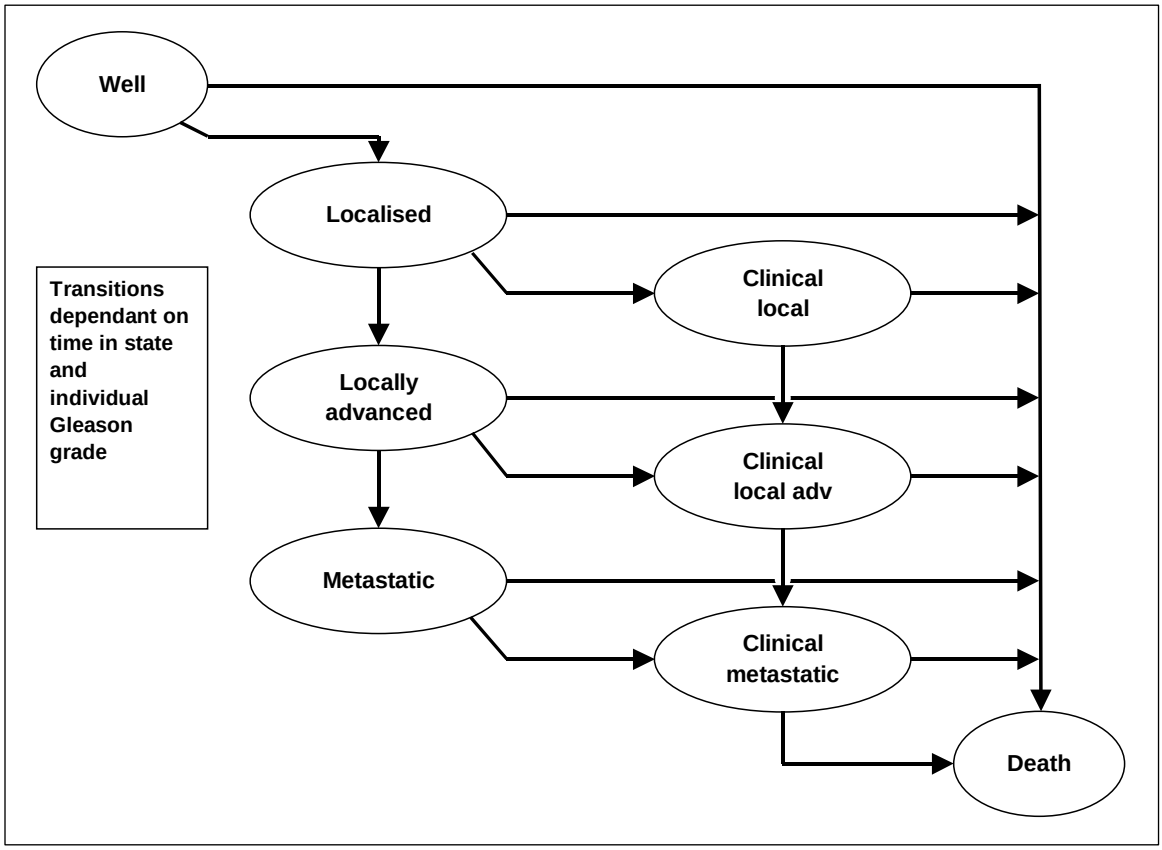
Table 6. Definition of states in model

Cancer stage categories	TNM stage
Local	T1-2; N0, NX; M0, MX
Locally advanced	T3-4; N1; M0, MX
Metastatic	Any M1

Individuals may die of other cause mortality from any state in the model and may be diagnosed clinically from any of the preclinical cancer stages. The model assumes that a proportion of individuals may develop prostate cancer at some point in their

lives. For those who develop prostate cancer the first incidence age of detectable preclinical cancer is assumed to follow a Weibull survival distribution from birth. At onset of disease proportions of patients are assumed to develop slow medium and fast progressing cancer as characterised by the Gleason score groups G<7, G=7 and G>7, the proportions in each group are parameters within the model. The dwell times in each of the preclinical disease states are similarly assumed to follow Weibull distributions. For local cancers the baseline dwell time is for the G<7 group, the G=7 group are assumed to have a relative hazard compared to the G<7 group and the G>7 has a relative hazard compared to the G=7 group. This modelling of sequential relative hazards assures a good correlation structure within the model. The shape parameters for locally advanced and metastatic disease states are assumed to be equal.

Figure 1. Natural history model of prostate cancer



Individuals with prostate cancer may be diagnosed clinically at any point after onset. The model assumes that the risk of clinical diagnosis is proportional to the risk of progression to the next disease state (or PCa death for those in the metastatic disease state), but that the two processes act as competing risks. This model allows the risk of clinical detection to increase with the age and stage of the cancer and also to be related to the aggressiveness of the disease for individuals as captured by the underlying Gleason grade.

The subsequent survival of patients through to death from prostate cancer or death from other causes is included in the model. If an individual is diagnosed clinically or through screening then a relative hazard associated with treatment is applied to the remaining time in the existing and subsequent cancer states. A common treatment relative hazard is modelled for local and locally advanced disease, with a separate relative hazard for metastatic disease. The local and locally advanced disease states are grouped here because of the availability of evidence with which to calibrate the model. The treatment of screen diagnosed cancers is modelled similarly to clinically diagnosed cancers with the exception that a different relative hazard for treatment is allowed for those individuals screen detected in the local disease state.

5.3 Calibration

All proportions, Weibull parameters and relative hazards in the natural history model are estimated by Bayesian calibration to prostate cancer data from the UK and from the ERSPC trial. A Metropolis Hastings algorithm has been used for this calibration.[64] This method generates multiple sets of parameters from their joint posterior distribution compatible with the observed data. The calibration was implemented using Microsoft Excel 2007 (Version 12.0)[65] with Visual Basic (Version 6.5) dynamically linked to the Simul8 patient level simulation.[63] Proposal sets of parameters were generated in Excel, these were passed to the Simul8 prostate

cancer model to estimate model outputs. The outputs were compared to observed data to estimate model fit and acceptance of proposed parameter sets. The iterative processing was managed by Visual Basic. The results were subsequently examined for convergence.

The advantages of this strategy are that it draws efficiently from a high dimensional correlated parameter space. Using this method the parameter sets are drawn according to their posterior probability given calibration data and thus they correctly summarise the residual uncertainty in the parameter space.

Disease natural history and epidemiology parameters were calibrated to the UK population using the ONS age specific cancer incidence data for 2004,[66] Eastern Region Cancer Registry stage and Gleason score distributions[67] under no screening and recruitment data from the ProtecT trial of prostate cancer treatment. (Personal communication Athene Lane, April 2010 Data from the Rotterdam section of the ERSPC trial were also used to inform the natural history parameters and PSA/biopsy test characteristics.[31,32,50] Differences between disease onset characteristics between the UK and Rotterdam populations were allowed by the inclusion of an adjustment parameter for the underlying time to onset of disease. Separate models based upon the ProtecT data and Rotterdam data respectively gave highly consistent estimates of the underlying probability of cancer parameter, indicating that a single adjustment parameter would be sufficient to capture these population differences. UK age specific other cause mortality estimates were obtained from the ONS using data from 2004.[68]

Initial calibration exercises converged to very low screening test sensitivities for both local disease and locally advanced/metastatic disease, in the region of 0.3-0.4. These have therefore been constrained to lie in the regions [0.5, 1.0] and [0.6, 1.0] respectively.

The best fitting set of parameters for the model and 95% credible intervals estimated from the Metropolis Hastings algorithm are given in Table 7. The correlation matrix for the parameter is presented in Appendix C.

Table 7. Model PCa natural history parameters

	Best fitting set	Lower 95% CI	Upper 95% CI
Probability of developing PCa	0.2241	0.2012	0.2452
Age of preclinical incidence - Weibull scale	64.0218	63.9178	66.0833
Age of preclinical incidence - Weibull ln(shape)	2.3525	2.1980	2.4479
Probability of initial PCa G<7	0.6812	0.5867	0.7019
Probability of initial PCa G=7 given not G<7	0.5016	0.3468	0.5673
Dwell time in local PCa - Weibull scale	19.8617	18.6158	19.8852
Dwell time in local PCa - Weibull ln(shape)	1.0353	0.7997	1.1845
Relative progression hazard for G=7 compared to G<7	1.3874	1.3384	1.4628
Relative progression hazard for G>7 compared to G=7	1.4027	1.2956	1.4157
Dwell time in locally advanced PCa - Weibull scale	16.3863	15.7460	20.5046
Dwell time in locally advanced PCa - Weibull ln(shape)	1.4404	1.3141	1.5015
Dwell time in metastatic PCa - Weibull scale	1.4242	1.1269	1.5049
Relative hazard for clinical diagnosis - local	1.1308	0.9937	1.2751
Relative hazard for clinical diagnosis - locally advanced	0.5900	0.5478	0.6638
Relative hazard for clinical diagnosis - metastatic	1.3147	1.0837	1.3782
Sensitivity of screening test for local disease	0.5602	0.5000	0.7570
Sensitivity of screening test for locally advanced / metastatic	0.7152	0.6000	0.9416
Relative hazard for treatment in local and locally advanced	0.6068	0.4686	0.7997
Relative hazard for treatment in metastatic disease	1.0239	0.8675	1.1722
Relative hazard for treatment in screen detected local disease	0.9367	0.8695	1.0638

Full details of the calibration results are included in Appendix H. Figure 2 shows the age specific incidence of prostate cancer and rate of death from prostate cancer recorded in the ONS data for 2004 compared to the predicted values from the model with no organised screening. The ONS age specific incidence figures together with figures from Eastern Region Cancer registry are detailed in the Appendix and give the overall stage and Gleason score distributions for that cancer registry published in Moore *et al.*[67] It should be noted that the age profile, not reproduced here but available in the above paper, follows closely the overall 2004 incidence figures from

the ONS, indicating that the Eastern Region population is representative of the overall UK population in terms of PCa incidence. Table 8 gives the estimates obtained from the model relative to the results from ProtecT trial (relative values are presented to maintain confidentiality of ProtecT) for the overall incidence of prostate cancer, age profile, stage and Gleason grade distributions.

Figure 2. Age specific incidence of prostate cancer

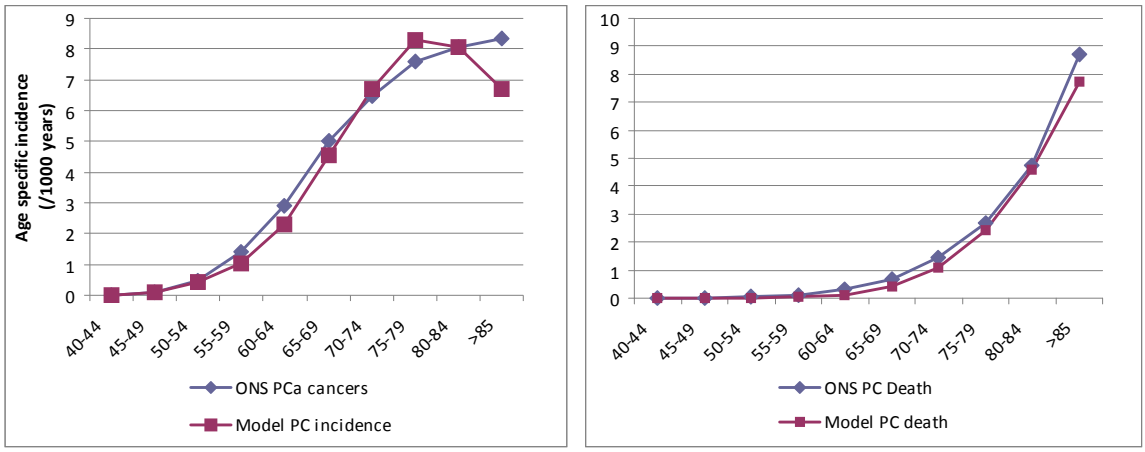


Table 8. Calibration results for ScHARR model against ProtecT data

[redacted]

The Metropolis Hastings algorithm provides a good fit of the model to the whole of the calibration data. The age specific cancer incidence closely matches the ONS

data up to the age of 80+ where after the model first over and then underestimates age specific incidence. The model reflects very closely the overall pattern and level of deaths from prostate cancer. The poorer fit in prostate cancer incidence in the elderly population may arise from the structural assumptions inherent in the use of a fixed proportion of people getting prostate cancer together with the use a Weibull distribution to model time of onset of detectable disease.

It was hypothesised that the pattern of prostate cancer incidence falling off in the older age groups, together with continued increases in prostate cancer deaths might arise from a monotonically increasing rate on onset together with reduced rates of diagnosis in the over 80's. An alternative model structure reflecting possible age specific diagnosis patterns was developed, but does not result in improved model performance, requiring additional parameters with increased complexity and little improvement in overall model fit.

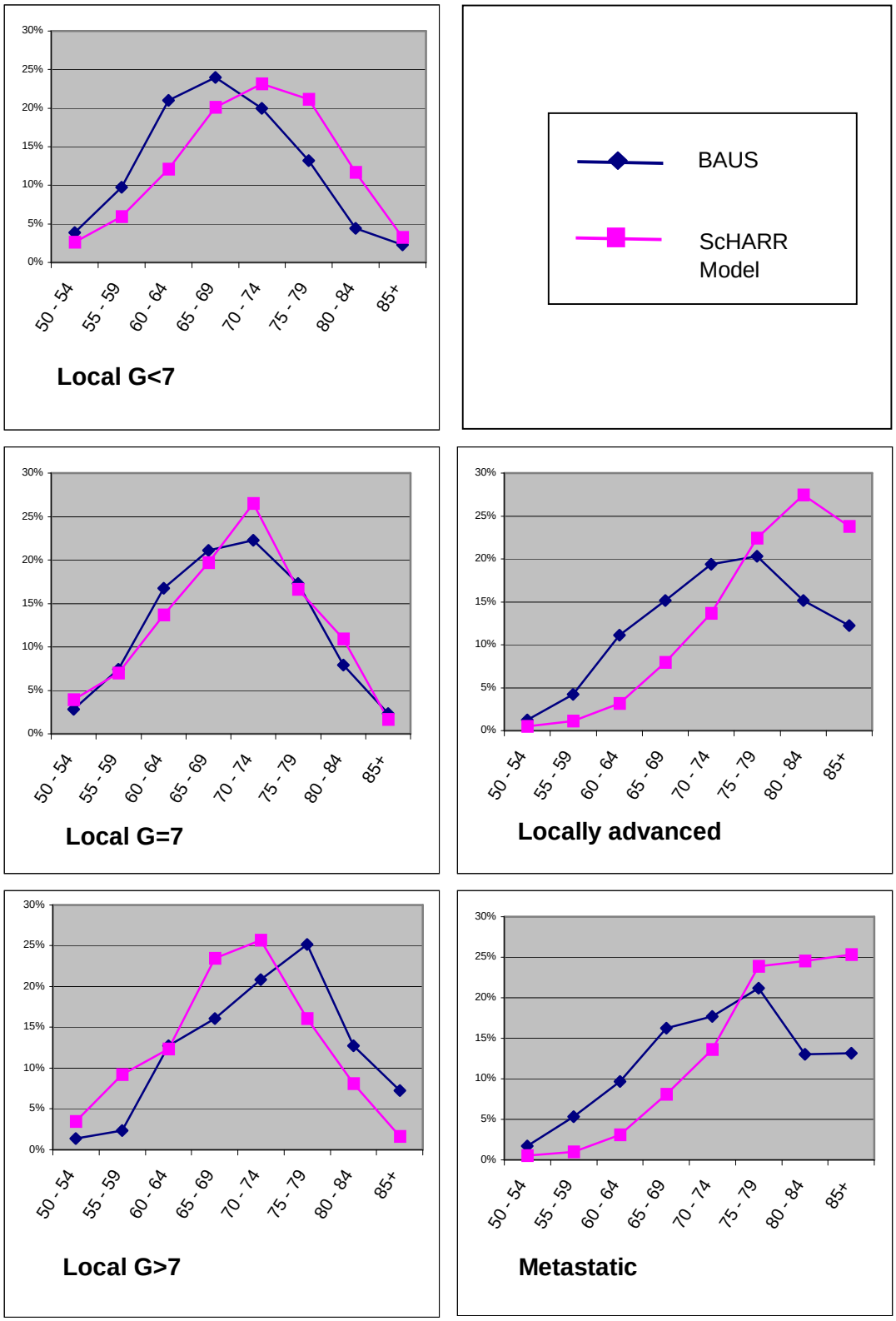
The Eastern Region stage distribution is matched well by the model, however the locally advanced and metastatic disease stages are grouped into an advanced category. The model tends to overestimate the proportion of cancers clinically detected with a Gleason score < 7 and underestimate those with a Gleason score of 7 in the no screening group reflected in the Eastern Region Cancer Registry data.

With regard to the calibration against the ProtecT recruitment data the age distribution of cancers identified through screening is well matched by the model. However, the model tends to overestimate the proportion of cancers occurring in the advanced group (locally advanced and metastatic) and tends to overestimate the proportion of cancers occurring in the G=7 Gleason group.

5.4 Model Validation

The model has been validated against the BAUS cancer registry for 2008. The distribution of cancers across age stage and Gleason grade is presented in Figure 3 and provides good validation for the model. It should be noted that the BAUS Registry data covers a different time period from the ONS Registry data used in calibration hence this validation does not simply represent the capability of the model to reproduce data used in its generation. Furthermore it should be noted that most of the data giving information on stage and grade progression comes from the screening arm of the ProtecT study rather than the ONS registry data. In light of these factors this validation provides good support to the structure and parameterisation of the ScHARR prostate cancer screening model.

Figure 3. Validation of ScHARR PCa model against BAUS Registry



5.5 Discussion

The Metropolis Hastings algorithm provides a good characterisation of the parametric uncertainty in the model, however uncertainties associated with structural assumptions in the model are not captured in this methodology. Thus the best example of this is in the poor fitting of age specific incidence in the higher age groups, as mentioned previously this probably arises from the use of the Weibull distribution for the duration in the well state, together with the use of a proportion of people prone to cancer at some point in their lives, together with the assumed fixed test characteristic sensitivities for the PSA/biopsy screening test.

Several simplifications from a more complex conceptual model of the disease natural history have been made in arriving at the implemented model structure. These simplifications arise principally from compromises necessary in using available data and in balancing the complexity of the model with the complexity of the decision problem.

Initial modelling work identified the need to investigate alternative models of disease onset. A model using a minimum age of onset with subsequent Weibull distributed time of onset has been investigated, together with an age related hazard of diagnosis. However, this model required more parameters and did not improve the overall fit of the model; consequently the simpler model has been retained as the baseline. This alternative model of the natural history is important as it has the potential to impact on decision making as it would suggest a higher level of underlying prostate cancer in the older age groups that might potentially be discovered by screening. Further evidence would be required to investigate this potential model structure adequately.

The model has been used to jointly estimate disease natural history and screening test characteristics. The calibration algorithm initially converged to very low test

sensitivities (in the region of 0.3). Whilst evidence for diagnostic test characteristics is often problematic being based upon poor ‘gold standard’ tests, the view was taken to constrain the test sensitivities to values more in line with other existing evidence. This however remains an area for further investigation either by including in the model additional data specifically on test characteristics and recalibrating the model and/or by investigating different models of disease natural history that result in consistent interpretations of the existing evidence.

The local disease state is a very broad classification, in order to better reflect subsequent treatment and survival impacts it would be preferable to include as a minimum separate states for T1 and T2 categories. This however is not possible with the current available evidence.

6. The screening impact model

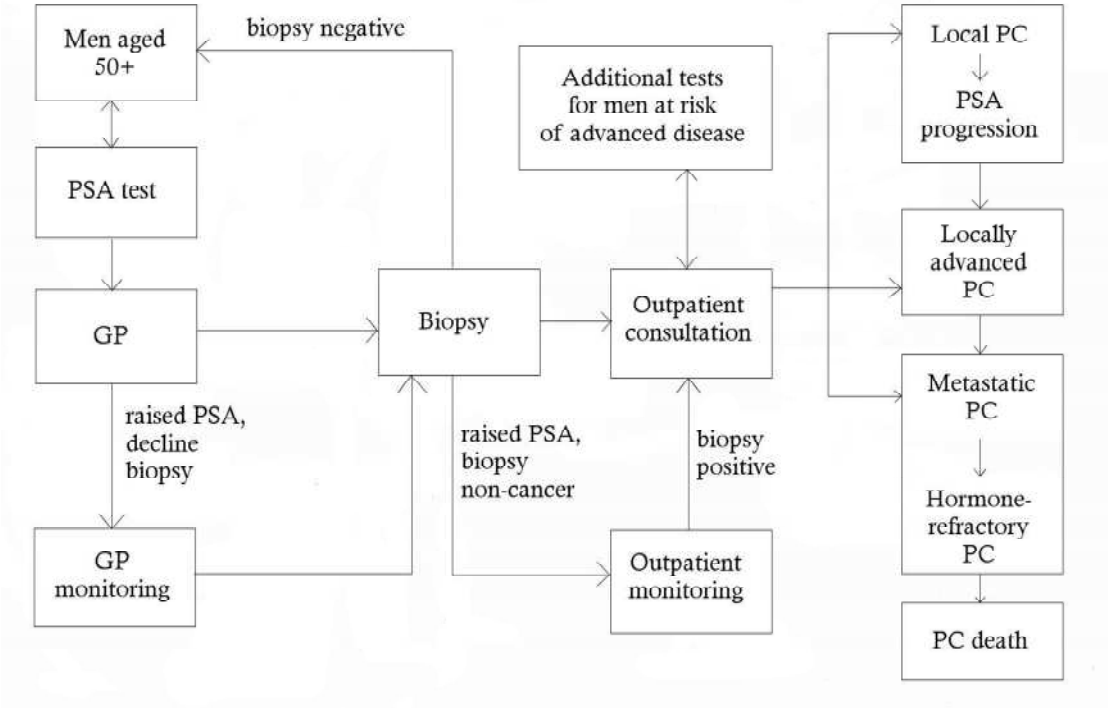
6.1 The Model

The natural history models estimates the number cancers detected, their severity and progression through the underlying disease states of local, locally advanced and metastatic cancers. This section describes a model to assess the impact of screening, diagnosis and treatment of detected cancers on incremental resource use, costs, and harms to men from the adverse effects of treatment. Two additional states of relevance only to detected cancers are added to the natural history model: PSA progression for patients diagnosed with local disease, and hormone-refractory metastatic cancer. All men with cancers, whether diagnosed or not, are input from the natural history model, so the same number of men are included for all screening policy options. The impact model is not an individual level simulation, but treats each man as a cohort with the characteristics of the individual (age, stage of diagnosis etc.) and assigns appropriate proportions of treatment, adverse effects and resulting costs. The summation of outputs over all men show the results of different screening policies on treatment patterns, adverse effects of treatment, resource use, costs, and QALYs for the cohort of men. The screening, diagnosis and treatment pathway used in the model is shown in Figure 4.

The population of concern is UK men aged 50 years and over. They may currently request a PSA test, or if a screening programme were to be implemented they would be offered the test. It is assumed those who test positive would consult their GP to discuss the result and consider whether they wish to proceed to biopsy. Some men, particularly those with a relatively short life expectancy, may chose not to have a biopsy and are monitored by their GP. Most men will however have a biopsy, and those who have a cancer identified are referred for a specialist consultation of their treatment options. Some of these men who are considered at risk of having

advanced cancers (spread beyond the prostate) will be referred for additional tests to ascertain the extent of the disease. Men with a positive PSA test but cancer-negative biopsy are considered at increased risk of disease, and may be monitored including further biopsy. Men with cancer will have a range of treatment options dependent on the extent (localised, locally advanced, metastatic), and aggressiveness of their disease, as reflected by their Gleason score (G<7, G=7, G>7). Once detected, men may progress through to more advanced cancer states, eventually dying of prostate cancer, or die earlier of other causes.

Figure 4. The screening, diagnosis and treatment pathway



The model includes the resources and costs for the diagnosis and treatment of disease. The numbers of men who are affected by adverse effects of diagnosis or treatment are estimated, and quality-adjusted life years (QALYs) for the cohort of men calculated for each screening policy option.

All costs and QALYs were discounted at a rate of 3.5% per year[69] to age 50 using a continuous discounting function.

6.2 Data

The data used to populate the model is described in four sections:

- Estimation of the resources required to diagnose cancers
- Treatment resource use and costs
- Adverse events associated with diagnosis and treatment of prostate cancer
- Utility values for the estimation of QALYs

6.2.1 Estimation of the resources required to diagnose cancers detected by a screening programme

The natural history model, previously described, estimates the numbers of men screened and screen and interval cancers detected at different ages according to the screening policy. The impact model estimates the number of screened men who have a positive test and those going on to, or refusing, biopsy using age-specific ratios from unpublished ProtecT trial data (2001-2007) (personal communication Athene Lane, April 2010).

The impact model estimates, for the background policy of no screening and for interval cancers, the number of PSA tests to identify the cancers detected, assuming the same ratio as for screened men, also using age-specific ratios from the ProtecT data. This may overestimate the number of PSA tests required to identify these cancers as a proportion of these patients are likely to have symptoms of PCa which prompt the test.

The overall ratios from the analysis of ProtecT data are similar to those reported by Moore from the ProTect study: of 94,427 participants 8,807 (9.33%) had raised PSA levels and 2,022 cancers were found, which is 23.0% of those with raised PSA.[67] The overall biopsy refusal rate from the data analysis was similar to the rate reported from the ProtecT feasibility study (12%)[3], and the overall rate from the ERSPC(14.2%).[1]

Note all these figures are derived from clinical trials and therefore may not reflect men's behaviour outside of a trial.

The ProtecT study only recruited men aged 70 years or less. To estimate ratios for older men linear models were fitted to the age-specific summary data.

6.2.2 Resource Use and Costs

All costs shown below are 2009/10. Where source costs relate to an earlier year they have been inflated using the Hospital & Community Health Services pay and price inflation index.[70] The model includes the costs of screening, diagnostic tests, radical treatment and the cost of ongoing treatment and monitoring, as well as terminal care costs for men dying of prostate cancer. Costs of treating adverse effects of treatment are not included. Most of the costs are from the National Reference costs.[71] **Note the costs of administering a screening programme are not considered.** All impact model parameters, together with their sources and the distributions used for the probabilistic sensitivity analysis are shown in Appendix D.

6.2.2.1 Prostate cancer diagnosis

PSA screening test

It has been assumed that counselling and the blood sample are done by a GP practice nurse in an average session of 16 minutes, at a cost of £10.73.[70] Additionally there is the cost of the PSA test itself of £11.81. Thus the total cost of PSA screening is £23.

Discussion of positive PSA test result

It is assumed that patients with a positive PSA test will see their GP to have a DRE and discuss the results, and how to proceed. The cost of a GP surgery consultation is £39.[70]

Monitoring of men who have a positive PSA test but decline biopsy

It has been assumed that these men will be monitored twice yearly by their GP with a PSA test, at a cost of £99.

Biopsy

The cost of a biopsy is taken from the National Tariff costs 2008/9.[72] The 2009/10 cost is £307 including the average market forces factor. It is assumed that this cost includes the results being reviewed by a urological cancer MDT as the 2008 NICE cancer guideline recommends.[7] The cost of an inpatient admission for the very small proportion of patients who are admitted to hospital with infection following biopsy is taken from the National Reference costs as a non-elective long stay (4.7 days) for major infection without complications: £2442.[71]

Additional diagnostic tests

For men with high grade (Gleason score >7) or locally advanced (T3/4 or N1) cancers it is assumed they have a bone scan (£173) and an MRI scan (£211), at a total cost of £384.

Monitoring of patients with raised PSA but negative biopsy

There is no standard management of these men. It has been assumed that on average men will have an additional three outpatient appointments, including PSA test, and one further biopsy, at a total cost of £728. The cost of an outpatient appointment is taken from the National Reference Costs 2008/9.[71]

Information Appointment

For men diagnosed with cancer it is assumed that they have an outpatient appointment to receive their diagnosis and consider treatment alternatives, at a cost of £133. Note it is assumed that the costs of patient review by an MDT, as

recommended in the NICE guideline “Improving Outcomes in Urological Cancers 2002”,[73] are included within the HRG costs of patient hospital attendances.

6.2.2.2 Treatment of localised cancers

Patients have a choice of several therapies. Only the most common (radical prostatectomy, radical radiotherapy (with or without hormone therapy), hormone therapy, watchful waiting and active monitoring) are considered. Two data sets were analysed to identify the proportions of patients of different ages and disease severities choosing different treatments. One data set was national cancer registry data collated by the South-West Public Health Observatory (personal communication Luke Hounsome, Oct 2009). The second data set was obtained from the British Association of Urological Surgeons (BAUS) for 2008 (personal communication Sarah Fowler, Feb 2010). The data and its analysis are described in more detail in Appendices E (BAUS) and F (registry). Both data sets included significant proportions of men (~20%) with no record of treatment. The BAUS data was used in the model, as it appeared more reliable. The registry data has no record of men on watchful waiting or active monitoring, and, contrary to clinical opinion, shows a high proportion of men with known treatment having RP (33%) compared to RT (18% - including combination with HT therapy).

The BAUS data showing the proportion of patients with localised cancer of different ages and Gleason score choosing each treatment is shown in Table 9. Note that the data is a sample of the population of men with prostate cancer and may be subject to biases. In particular it is possible that the proportion of patients having radical prostatectomy is overestimated, as being an inpatient procedure it is routinely recorded within the Hospital Episode Statistics, whereas the other treatment modes are not. The proportion having prostatectomy in the BAUS data is however lower than that reported in the ERSPC trial (53% overall),[1] although that data may also be

biased by missing data (18% treatment unknown), and will also depend on varying treatment preferences between countries.

Table 9. Current treatment patterns for localised cancers by Gleason score and age (BAUS 2008)

Age	Gleason score	N	RP	RT	HT	RT + HT	AM / WW	Other / Unknown
< 70	<7	1,575	22.2%	8.9%	2.6%	4.8%	28.1%	33.4%
	7	1,006	28.5%	5.4%	11.5%	16.0%	6.2%	32.4%
	>7	292	14.7%	2.4%	30.1%	17.8%	2.4%	32.5%
	Total	2,873	23.7%	7.0%	8.5%	10.1%	17.8%	33.0%
70-79	<7	881	3.3%	4.5%	9.2%	9.2%	40.2%	33.6%
	7	847	4.0%	5.0%	22.2%	20.8%	14.0%	34.0%
	>7	422	1.7%	1.4%	44.8%	18.7%	3.1%	30.3%
	Total	2,150	3.3%	4.1%	21.3%	15.6%	22.6%	33.1%
>= 80	<7	187	0.0%	0.0%	16.6%	1.1%	49.7%	32.6%
	7	201	0.5%	0.0%	42.3%	1.5%	25.4%	30.3%
	>7	178	0.6%	0.0%	60.1%	0.6%	7.3%	31.5%
	Total	566	0.4%	0.0%	39.4%	1.1%	27.7%	31.4%
Total	<7	2,643	14.3%	6.8%	5.8%	6.0%	33.6%	33.4%
	7	2,054	15.7%	4.7%	18.9%	16.6%	11.3%	32.9%
	>7	892	5.7%	1.5%	43.0%	14.8%	3.7%	31.3%
	Total	5,589	13.5%	5.2%	16.6%	11.3%	20.6%	32.9%

An “other” category is explicitly included in the model, as assigning these pro-rata to the known categories may overestimate particular treatments if there is bias in the missing data, for example better recording of active treatments over monitoring. However, for the purposes of estimation of resource use, costs, adverse effects of treatment and QALYs an assumption had to be made regarding treatment and for the deterministic analysis they were assigned pro-rata to the known categories. Sensitivity analysis was used to explore the effects of alternative assumptions. Note that the data shows patients with non-aggressive cancers (G<8) on hormone therapy, contrary to current guidance.[7] It is not known to what extent some clinical practice is at variance with the guidance, or whether it the data is inaccurate. For the baseline it is assumed that men with localised PCa and G<8 recorded as having HT alone all had active monitoring or watchful waiting, and men shown to have RT+HT just had RT. A sensitivity analysis was done with the data as shown in Table 9.

The BAUS data does not distinguish between active monitoring and watchful waiting. The proportions choosing each have been estimated by assuming men aged less

than 70 years will choose active monitoring and men aged 70 and over will be on watchful waiting. In fact the decision is not solely determined by age, but by a man's life expectancy, taking into consideration serious comorbid diseases.

Radical treatment

The cost of a radical prostatectomy is taken from the National Tariff 2008-09, inflated to 2009/10, which is £4,547.[72] The costs of radiotherapy are taken from the National Reference costs 2008/9 and include the cost of a planning session and delivery of 37 fractions of radiotherapy, at a total cost of £5,381. For patients with localised cancer having a combination of radiotherapy and hormone therapy, hormone therapy is assumed to comprise a neoadjuvant course of the LHRHa goserelin for six months.

All patients are assumed to have an outpatient visit for initial post-treatment monitoring (including PSA testing). More frequent monitoring in the first two years following treatment than subsequently is accounted for by including a further two outpatient visits in the cost of treatment. Thus the total costs are:

Radical prostatectomy	£4,956
Radical radiotherapy	£5,790
Radical radiotherapy with neoadjuvant HT	£6,325

Follow up of patients following radical treatment

It has been assumed that men will be seen in an outpatient setting twice yearly. The 2008 NICE guideline indicates that after at least two years men may be monitored by their GP, but this recommendation is controversial, and clinical advice suggests that in practice most men are followed up on an outpatient basis.

Watchful waiting

Watchful waiting is more often chosen by older men or those with significant comorbidities whose cancers are unlikely to progress much during their lifetimes. The

objective is to monitor the patient for disease progression, which is then usually treated with hormone therapy. It has been assumed that these men see their GP twice a year for monitoring and a PSA test, at a total cost of £99.39 per year.

Active monitoring

The frequency of monitoring required, the tests that should be performed routinely and the criteria that should initiate consideration of radical treatment are poorly defined. In a systematic review of active monitoring which included 5 studies, all study protocols included repeat PSA tests and DRE at three to six month intervals, three included biopsy either annually or twice yearly, and some included additional tests such as bone scans.[25] The NICE prostate cancer guideline merely recommends that men should have at least one further biopsy.[7] It has been assumed that these men are monitored four times a year in an outpatient setting, with on average a biopsy every two years, at a total cost per year of £684.

Some studies of active monitoring show a high proportion (up to 50%) of patients opting for radical therapy within two years.[25] The proportion of patients abandoning active monitoring will clearly depend on their initial selection and their and their clinician's confidence in monitoring. A UK study which included some intermediate as well as low risk patients reports a rate of approximately 10% of patients who went on to radical therapy within two years.[26] This rate is used in the model, and it is assumed that patients who have radical therapy have radical prostatectomy and radiotherapy in the same proportion as those who have immediate radical treatment,

Hormone therapy

The costs of hormone therapy for patients with localised disease are estimated by the same method as for locally advanced disease, described in section 6.2.2.3.

Post- PSA Progression

Patients who experience PSA progression in localised disease receive additional monitoring. It is assumed these men have an additional 4 outpatient visits, and a bone and CT scan every 2 years, at an annual cost of £689. The average time from PSA progression to locally advanced disease has been estimated as 2.6 years from data reported by Kestin.[74] These costs are applied to men who are diagnosed with local disease who are not treated first line with hormone therapy, who progress to locally advanced disease. It is assumed they do not commence hormone therapy until progression to locally advanced disease.

6.2.2.3 Treatment of patients diagnosed with locally advanced disease

The BAUS data showed that the majority of men in this group (87%) for whom treatment was recorded have hormone therapy alone or with radiotherapy. These are the only treatments for locally advanced disease which are considered in the model. Radiotherapy should be given with neoadjuvant hormone therapy for three to six months. Patients with high grade disease (Gleason score >7) should also have adjuvant therapy for a minimum two years following RT.[7] Data from BAUS[75] was used to estimate the proportion of patients having either hormone therapy alone or combination hormone and radiotherapy, as shown in Table 10.

Table 10. Treatment choice by age for locally advanced cancers (BAUS 2008)

Age	N	HT	RT + HT
< 70	572	74.0%	26.0%
70-79	770	79.6%	20.4%
>= 80	541	98.2%	1.8%
Total	1,883	57.3%	11.5%

Only a relatively small proportion of patients have radiotherapy. The treatment costs for this diverse group of patients have been estimated by assuming all patients are

on hormone therapy, with a small proportion (see Table 10) also incurring costs for radiotherapy. Whilst some patients who have radiotherapy will not be continuously on hormone treatment, other patients whose primary hormone treatment fails will have combined therapy.

Radiotherapy costs are assumed to be the same as for localized disease i.e. £5,790. The annual treatment costs for patients on hormone therapy are described below.

Annual treatment costs for patients on hormone therapy (local, locally advanced and metastatic tumours)

An analysis of Prescription Cost Analysis data for England shows that goserelin acetate, a luteinizing hormone-releasing agonist (LHRHa), is the most commonly prescribed hormone therapy for prostate cancer, and it is assumed for costing purposes that patients are all treated with goserelin.[76] Leuprorelin, another LHRHa is also sometimes prescribed, with similar costs. The use of anti-androgen therapy, principally biclutamide, appears less common, and is not recommended for patients with metastatic cancer.[7] Bilateral orchidectomy is an alternative method of achieving androgen withdrawal, but the numbers of men having orchidectomies has been falling.[7]

LHRHas cause androgen withdrawal, and are given by injection, most commonly every three months. The cost of a three-monthly dose of goserelin acetate (10.8mg) is £267.[77] Additionally, patients having LHRHas will need to see a health professional to have their three-monthly injection. It is assumed this is done by a GP practice nurse at a cost of £11.81 per visit.[70] All patients are monitored on an outpatient basis twice yearly and on average it has been assumed they will have a Dexa scan every two years (£75.06).[71] The total annual costs for hormone therapy are shown in Table 11.

Table 11. Annual costs of hormone therapy

Item	Cost 2009/10	Number/year	Annual Cost
Nurse (GP practice)	£11.81	4	£47.22
Goserelin (Zoladex LA) 10.8mg syringe	£267.48	4	£1,069.92
Outpatient visit	£132.64	2	£265.28
Dexa scan	£75.06	0.5	£37.53
Total			**£1,419.96**

6.2.2.4 Treatment of patients with hormone-refractory disease and terminal prostate cancer

The costs of treatment and terminal care are taken from an economic analysis of the TAX327 trial of docetaxel chemotherapy in patients with hormone-refractory metastatic cancer in comparison to other therapies.[78] Docetaxel with prednisolone is the only chemotherapy regime licensed for use in hormone-refractory prostate cancer. The analysis was based on resource use in the TAX327 trial, and included the costs of chemotherapy, palliative and terminal care. Whilst not all men will receive chemotherapy, the majority do, and the costs are likely to be a reasonable representation of the costs of care in the final months of life.

Collins and colleagues[78], reports the total cost of care in 2003/4 (with mean survival 1.9 years) to be £15,833, including a cost for terminal care of £3,528. These costs, inflated by the Hospital and Community Health Services inflation index[70] to 2009/10 costs, gives an annual cost of care of £7,909 and a terminal care cost of £4,308. Costs of hormone refractory treatment are allocated to men who die of prostate cancer in the metastatic disease state, who are not diagnosed at death. The cost of terminal care is allocated to all men who die of prostate cancer.

6.2.3 Adverse effects of screening and diagnostic tests for prostate cancer

PSA test and DRE

The PSA test entails taking a blood sample. Adverse effects are mild (dizziness, bruising and haematoma) and extremely rare: 26.2 per 10,000 tests. DRE similarly very rarely leads to bleeding and pain (0.3 per 10,000).[2]

Biopsy

Minor adverse events are relatively common. In a systematic review of biopsy methods rates of hematospermia were reported to be 75% and 29% respectively for 10 core biopsies, which is the current UK standard. These rates are, however, derived from a single study, and rates for 12 to 13 cores show a range of 6% -82% for hematospermia and 1% to 23% for rectal bleeding.[22] In the ERSPC study, which used sextant biopsies, the rate of hematospermia was 50%, with 23% of patients having symptoms for more than three days.[79] Rectal bleeding was less common at 1.3%, but the results of the Eichler *et al.* review suggest that the incidence of rectal bleeding is associated with the number of biopsy cores.[22]

Major adverse events causing significant discomfort or additional treatment are much less common. Eichler *et al.* reports infection rates of 0.9% for 10 core biopsies (0.0 – 0.7% for 12/13 cores) and bleeding in 0.3-0.6 per cent of men.[22] Infection rates will vary according to the use of antibiotic prophylaxis used. In the ERSPC study all men were given prophylaxis both prior to and post-biopsy. Of these 3.5% developed fever, and 0.47% were admitted to hospital for intravenous antibiotic therapy, and recovered within days.[79]

6.2.4 Adverse effects of treatment for prostate cancer

Radical prostatectomy - mortality

Reviews suggest rates of mortality within 30 days of radical prostatectomy of approximately 0.5%[8], [28]. A recent large population based analysis of over 11,000 Canadian men shows a similar overall rate (0.48%), but that the absolute excess mortality risk varies by age: 0.18%, 0.51% and 0.59% for men aged 50-59, 60-69 and 70-79 respectively, although the relative risk of mortality compared to men of the same age was consistently a factor of 9.[80]

Urinary symptoms, rectal toxicity and sexual dysfunction

It is known that many treatments for prostate cancer result in adverse effects, particularly urinary incontinence, rectal toxicity and sexual dysfunction. Published rates of such adverse effects however vary widely, and are dependent on many factors including how the adverse events are measured, the time from treatment, and differences in therapeutic technique. They may also be confounded by baseline and underlying malfunction. The tables below summarise results from two systematic reviews,[27;28;81] as well as from two large population based studies, one from the US (the Prostate Cancer Outcomes Study)[82;83], and the other from Australia.[84] The population studies are of particular interest as they use common outcome measures across different treatment modes, and report longer term outcomes (two and five years for the PLCO, three years in the Australian (Smith *et al.*) study[84]. The model only considers the long term adverse effects of treatment. Being population cohorts (as were most studies included in the reviews) there were biases in patient selection between treatments such as age and co-morbidities, but both studies report analyses which adjust for these, although the adjusted Smith analysis is not in a form appropriate for the model. Despite this disadvantage the results of the Smith study were used in the model, unless otherwise stated. Not only is the study much more

recent than the PLCO data, thereby reflecting more recent treatment techniques, it includes active monitoring and hormone therapy as well as the radical treatment options. Although fully adjusted rates for baseline characteristics were not shown, baseline malfunction was reported as well as three years post diagnosis, allowing the incidence of adverse events in the proportion of patients not affected at baseline to be estimated.

Urinary symptoms

Urinary symptoms include incontinence of varying degrees of severity, urethral stricture and hematuria. Whilst incontinence is more common following RP, urethral stricture and hematuria is less common that after RT.[28] The figures shown for the PCOS and Smith study relate to incontinence only (Hoffman *et al.*: leakage daily or more often;[82] Potosky *et al.*: no control or frequent leaks[83], Smith *et al.*: needing to wear one or more pads per day), whereas some studies in Hummel *et al.*[27] are for more general urinary symptoms (See Table 12).

Table 12. Rates of urinary symptoms following treatment for prostate cancer

		RP			RT (3DCRT)			WW/AM	HT
		Central	Range		Central			Central	Central
			Low	High		Low	High		
Hummel 2003		15	5	25	20 (20)	9 (9)	23 (23)	-	
Wilt 2008	-incontinence		5	35		2	6	-	
	-urethral stricture/hematuria	more common in RT than RP						-	
Hoffman 2003 PCOS 2 yr	- unadjusted	35			12			33	
Potosky 2000 PCOS 2 yr	- unadjusted	9.6			3.5				
	- adjusted	**9.8**			**3.3**				
Potosky 2004 PCOS 5 yr	- unadjusted	14			5			-	
	- adjusted	15			4			-	
Smith 2009	baseline	1.1			0			6	7
	3 years	12.3			2.7			3.4	4
	difference	**11.2**			**2.7**			**-2.6**	**-2.3**

Potosky *et al.*[83] reports variation of an incontinence summary score (UCLA index) with time for both RP and RT. For men with normal baseline function the scores for men having RT drop from approximately 100 to 95 within the first six months, then remain constant. Following RP the scores fall to 60 in the first six months then recover somewhat to 75 over the following 18 months, then stabilising. These results

appear at variance with the difference between the two and five year results for incidence of incontinence, which is possibly explained by differences in definition.

The Hoffman *et al.* results show incontinence to be also high in patients choosing watchful waiting.[82] This may at least partially due to their greater age (predominantly over 70). In an RCT comparing RP with WW 49% and 21% respectively reported leakage at least once a week.[85] The Smith study shows very low levels of baseline incidence, a result confirmed in other recent studies. A study of lower urinary tract symptoms (LUTS) in men attending PSA screening showed 24% of men diagnosed with prostate cancer occasionally/sometimes suffered leakage, with only 0.5% having symptoms all the time.[86] The latter category would appear to be more congruent with the definition used by Hoffman *et al.*[82], indicating a negligible level of underlying morbidity for men aged 50 to 69 years. A population survey in Leicestershire and Rutland showed the prevalence of profound incontinence (at least daily wetting) to vary from 0.6% in men aged 50-59 to 3.6% in men aged 80 or more[87], but in a study associated with the ERSPC screening trial no relationship of urinary function with age (range 58 -78) was found.[88]

Conclusion

- Symptoms of incontinence are more common following RP than RT, and endure.
- The underlying level of serious morbidity in the population of older men is relatively small (<5%), and may be age-related.
- Although there is some variation in the study results, the adjusted figures for the two large population studies are similar. The three year results from Smith are used in the model. They will be assumed to have lifetime duration.
- It is unlikely that the reduction in symptoms seen in the Smith data for WW and HT are real effects: the effect is assumed to be zero. A sensitivity analysis was undertaken with the data as is.

Rectal toxicity

Rectal injury is recognised as risk for patients undergoing pelvic radiotherapy. Developments in radiotherapy from two dimensional to three dimensional conformal radiotherapy (3DCRT) and intensity modulated radiation therapy (IMRT) have been driven by the aim to increase radiotherapy dose (to improve survival) whilst minimising bowel toxicity.

Table 13. Rates of rectal toxicity following treatment for prostate cancer

		RP			RT (3DCRT)			WW/AM	HT
		Central	Range		Central			Central	Central
			Low	High		Low	High		
Hummel 2003 (bowel injury)		0	0	0	15 (5)	8 (2)	26 (12)	-	
Wilt 2008		rarely reported -less than RT				15	30	-	
Hoffman 2003 PCOS 2 yr	- unadjusted	14			29			16	
Potosky 2000 PCOS 2 yr	- unadjusted	14.5			35.7				
	- adjusted	16.1			30.5				
Potosky 2004 PCOS 5 yr	- unadjusted	17.7			33.4			-	
	- adjusted	19.3			28.5				
Smith 2009	baseline	4.4			10.6			13.5	10
	3 years	3.5			14.5			6.3	6
	difference	-0.9			3.9			-7.2	**-4**

The figures reported in Table 13 by Hoffman *et al.*[82] and Potosky *et al.*[29] are for urgency, but the prevalence of diarrhoea is similar. Potosky *et al.*[29] also reports a significant difference between RT and RP in painful haemorrhoids (20% compared to 10%). The five year figures indicate ongoing issues, but likely at a lower level of severity. They also indicate rectal morbidity in men who had RP, which the authors suggest reflect the prevalence of symptoms in the general population. The figures reported by Smith show much lesser morbidity in all patient populations[84]. It may be due to the measure – a self-assessment of the problem severity, which is closer to the bother measure in the PCOS study. The latter shows an adjusted incidence of bother of 4.1% for RP and 5.7% for RT.

Although the Smith *et al.* study is more recent, the measure used, combined with the negative values for treatments other than RT, in particular WW, suggest the data are not the most reliable for bowel toxicity. The difference between RP and RT rates from

Potosky (PCOS) adjusted 5 year results will be used as baseline for RT, i.e. 10%. For all other treatments bowel toxicity was set to zero.

Conclusion

An incidence of 10% for long term rectal toxicity was assumed for RT, and zero for other treatments. A sensitivity analysis was done using a rate of 3.9% for RT.

Sexual dysfunction

Sexual dysfunction is the most common adverse event associated with prostate cancer treatments.[28] Surgical techniques such as nerve sparing procedures have been developed with the aim of reducing toxicity. Smith *et al.* reports data for both nerve sparing and non-nerve sparing which show incident sexual dysfunction to be 21% lower for the former (80% compared to 59%), but nerve-sparing procedures are not appropriate for all cancers.[84] The figures shown in Table 14 are for all RP as reported by Smith *et al.*, which was comprised approximately 50:50 of the two procedures. In the UK, BAUS data records 46% of men having RP having a nerve-sparing procedure, but approximately a third of the remainder were unknown procedure. The higher rates of sexual dysfunction reported by Potosky *et al.* may be due to older data and a lower proportion of nerve sparing procedures. Nevertheless the data from the two population studies are reasonably consistent for RP.

Table 14. Rates of sexual dysfunction following treatment for prostate cancer

		RP			RT (3DCRT)			WW/AM	HT
		Central	Range		Central	Range		Central	Central
			Low	High		Low	High		
Hummel 2003		58	44	60	31 (36)	29 (32)	36 (39)	-	
Wilt 2008			5	95		5	95	-	
Hoffman 2003 PCOS 2 yr	- unadjusted	58			43			33	
Potosky 2000 PCOS 2 yr	- unadjusted	80			62				
	- adjusted	82			50				
Potosky 2004 PCOS 5 yr	- unadjusted	77			73			-	
	- adjusted	79			64			-	
Smith 2009	baseline	22			30			27	42
	3 years	77			68			54	98
	% didn't have at baseline affected*	**69**			**52**			**35**	**94**

*Assuming no men who were affected at baseline are cured, and adjusting for underlying increase with age

The two year results of the PLCO for RT are very similar to those of Smith *et al.*, but Potosky *et al.* for the PLCO reports continuing decline in erectile function with time for these men, resulting in a higher rate at five years. Impotence at five years was strongly associated with hormone therapy, but adjustment for it "did not materially alter the differences in sexual function observed between the treatment groups".[83]

Potosky *et al.* reports that whilst erectile dysfunction was higher at two years in the RP group compared to RT, (adjusted rates 82% and 50% respectively), the difference was much less at five years (79% and 64%).[83] Patients who had RT had a continuing decline in erectile function with time, whereas rates in men following RT were relatively stable.

The high level of dysfunction in men who chose watchful waiting could be attributed to high baseline malfunction in the older population more likely to choose watchful waiting, but this only applies to the Hoffman study.[82] The similarly high incidence in men not previously affected derived from the Smith *et al.* study may be due to psychological effects or progression to hormone therapy; the authors make no comment.[84] For consistency across treatments the Smith figures will be used, but a sensitivity analysis was undertaken with the incidence of sexual dysfunction for watchful waiting/ active monitoring set to zero.

There is good evidence that erectile dysfunction is also prevalent in the general population of older men. A systematic review reports rates in men younger than 40 years ranged from 2 to 9%. For men older than 70 years rates ranged from 10 to 71%, and for men older than 80 years prevalence ranged from 18 to 86%.[89] The authors comment on the difficulty of making comparisons between studies because of the differences in definitions used. One study included in the review that reported age-related rates is from the UK: a cross-sectional study of GP practices in Wales.[90] The rates it reports (for complete erectile dysfunction) are: age 55-60 7%, age 61-65

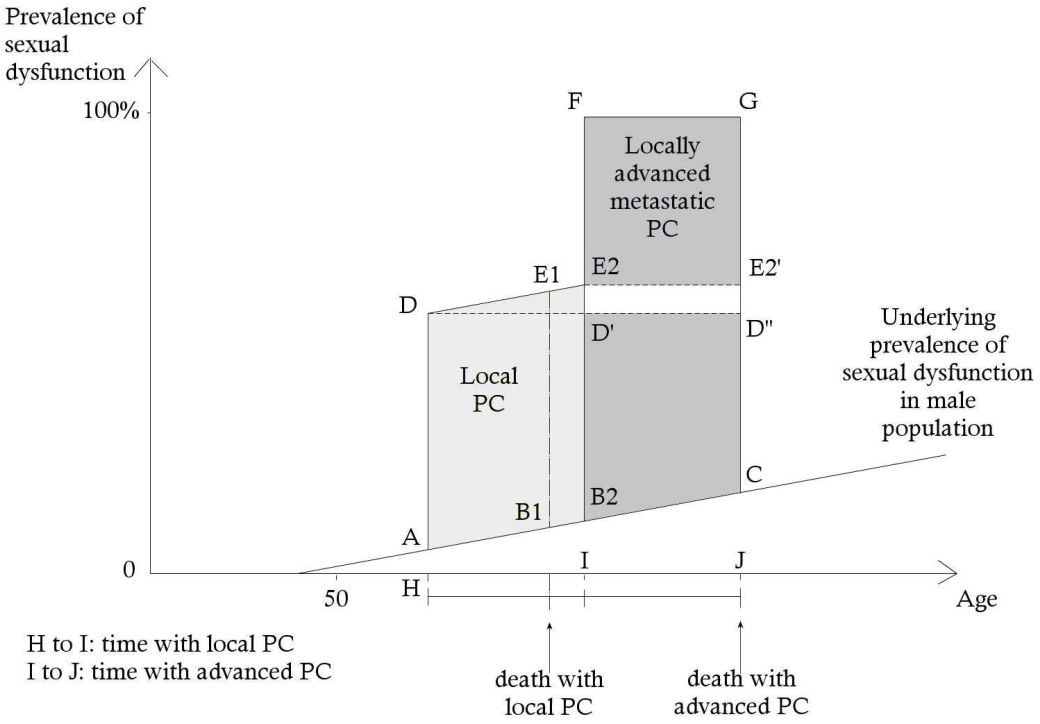
13%, age 66-70 22%. A study associated with the ERSPC with a larger population reports similar rates for total erectile dysfunction: age 58-61 12%, age 62-64 14.6%, age 65-67 18.4%, age 68-70 21.9%, age 71-78 26.3%.[88] Whilst most surveys include men with prostate cancer, the latter specifically excludes them.

The latter study data was used to estimate age-related underlying sexual dysfunction for men at the time of diagnosis. Incident sexual dysfunction resulting from treatment was then only applied to the proportion of men not already affected. Previous studies have applied incidence rates for sexual dysfunction resulting from treatment to all men, thus overestimating the adverse effect of treatment, particularly in older age groups. Similarly the total prevalence of sexual dysfunction (underlying and adverse effects of primary treatment) for men diagnosed with local disease who progress to locally advanced disease is calculated at the time of transition, so the effects of hormone therapy are only applied to the previously unaffected. Figure 5 illustrates the calculation. A linear function was fitted to the data so underlying sexual dysfunction could be calculated for all ages.

Calculation of the proportion of men differentially affected by sexual dysfunction resulting from treatment over time in the presence of an underlying increase with age

If it is assumed that the proportion of men with incident sexual dysfunction resulting from treatment is the proportion affected for life, the effect of treatment on sexual dysfunction is overestimated, as some men will develop sexual dysfunction anyway later on. Figure 5 shows how the proportion affected with time is calculated.

Figure 5. Illustration of the estimation of the effect of PCa interventions on the prevalence of sexual dysfunction with time



Firstly, if underlying sexual dysfunction is ignored, the proportion affected resulting from treatment for localised cancer for the duration of localised disease is represented by the rectangle H (time of diagnosis), D (incident sexual dysfunction resulting from treatment), D' and I (time of death or transition to locally advanced cancer.

However underlying sexual dysfunction increases with age, as represented by the line with points A,B,C. Thus for men diagnosed with localised cancer at age H a proportion, A, will already have sexual dysfunction. Of those not already affected a proportion represented by the line AD will have incident sexual dysfunction as a result of their PCa treatment. As not all men treated for localised cancer suffer SD following treatment, those as yet unaffected will continue to see an age related increase (point E2 at the time of transition to locally advanced disease). Over the same period of time the general population would have experienced an increasing prevalence to point B2. The differential proportion affected by prostate cancer

treatment is therefore represented by the trapezium delineated by A,D,E2,B2. At the time of transition to locally advanced disease most men will commence hormone therapy, and the majority of those not previously affected by SD will experience incident SD (line E2,F). The differential proportion affected over time with advanced disease is represented by the areas marked by E2, E2', F,G plus area B2,C,D',D''.

Conclusion

Although reports of the rates of erectile dysfunction following radical therapy vary widely,[28] the results of the two population studies are similar for RP and RT. The results of Smith *et al.*[84], which allow estimation of the incidence of sexual dysfunction resulting from treatment in men who were previously unaffected are used in the model. It is not clear whether the rates reported for active monitoring relate to the treatment itself or to progression to hormone treatment. The rate of 35% is used as baseline in the model, but a sensitivity analysis tests the effect of this by setting the value to zero.

Adverse effects of hormone therapy

Androgen ablation delays disease progression and palliates symptoms of progressive disease.[91] However, adverse effects are common. For androgen withdrawal (by LHRHa agonists or bilateral orcidectomy) short term effects are hot flushes, loss of sexual drive, weight gain and lethargy. Anti-androgen therapy has less effect on sex drive but may cause breast enlargement and pain (gynaecomastia, mastalgia).[7] A systematic review of single agent androgen suppression in men with advanced prostate cancer summarized only withdrawal from therapy as a marker of serious adverse event, commenting on the difficulty of summarizing data on adverse events due to the variation between trials in their measurement and reporting of events.[91] Withdrawal occurred less often for patients treated with LHRHa (0 – 4%) than antiandrogens (4 – 10%). However, the analysis included therapies which are less commonly used now in the UK. For the LHRHa goserelin and leuprorelin the

rates were 0 -2%, and for the anti-androgen biclutamide 4%. It should be noted however that the biclutamide dose was only 50mg daily, whereas the recommended dose for monotherapy is now 150mg daily.[91]

Long term adverse effects of androgen deprivation are also of concern. A systematic review has examined the long term effects of androgen deprivation on bone and cardiovascular outcomes.[92] A meta-analysis of five studies yielded a relative risk of fractures of 1.23 (1.10 – 1.38) for men on androgen deprivation compared with men with prostate cancer not on HT. The relative risk of vertebral fractures (from three studies) was 1.39 (1.20-1.60). An association was also reported between androgen deprivation and osteoporosis or lower bone mineral density in three included studies, although statistical significance was only reported in one. There was also increased risk of cardiovascular mortality in men having androgen deprivation, relative risk 1.17 (1.07 – 1.29).

Conclusion

The effects of hormone therapy on urinary, bowel and sexual dysfunction are as reported by Smith[84], and shown in Tables 12, 13 and 14. The long term effects of hormone therapy are not included in the model.

6.2.5 Utility values for prostate cancer states

Utility values represent preferences for different health states on a scale of 0 (death) to one (full health. Patient life years are weighted by utility values to calculate quality adjusted life years (QALYs). There are different methods of estimating utility values. The 2008 NICE methods guide states that the EQ – 5D is the preferred measure of HRQoL, and public preferences for health states should be elicited from a representative sample of the UK population using a choice based method.[69]

In a recent review of IMRT for prostate cancer a literature search was undertaken to identify utility values for prostate cancer states.[93] Only one study was identified that reported the utility values for adverse event states of PCa, and used the EQ-5D, and that was in a study of Japanese men (Shimizu 2008).[94] One further study was identified that reported utility values based on societal preferences using recognised instruments (Krahn 2003).[95] A further study reported the utility value of symptomatic metastatic hormone-refractory cancer using the EQ-5D in men from Europe, North America and Australia.[96] The previous literature search was updated for the time period May 2009 to March 2010 in the following databases: MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, DARE, HTA Database, NHS EED. The search strategy is shown in Appendix G. A total of 15 references were indentified after deduplication. No further relevant studies (studies reporting prostate cancer utilities based on patient reported health states valued by public preferences) were found.

The main design features of the two studies for adverse events of treatment are shown in Table 15, together with the ideal study characteristics for a UK perspective. None of the study designs are ideal. Whilst Shimizu used the EQ-5D instrument, as well as the SF -36, the patient states are reported by Japanese men, and may reflect different values to a UK population on various aspects of health. Thus although the Shimizu study is larger and therefore likely to yield more precise estimates of utility, they may not be accurate as applied to the UK population. The values of Canadian men might be expected to more closely match those of a UK population, but the QWB instrument uses a rating scale rather than a choice-based method to elicit public preferences. The HUI instrument uses both methods, using a choice based method to anchor the extreme ends of the scale and a rating scale for intermediate points. The utilities derived by Krahn *et al.* using the HUI instrument may therefore be considered to be the most relevant in the context of a UK model.

Table 15. Utility study design

	Patient population for HRQoL	N	Public preference population	Method of elicitation of public preference
Ideal				
EQ-5D	UK men	large	UK	Time trade off or standard gamble
Shimizu 2008				
EQ-5D	Japanese men	323	Japan	Time trade off
SF36	Japanese men		UK	Standard gamble
Krahn 2003				
HUI	Canadian men	141	Canadian	Rating scale and standard gamble
QWB	Canadian men		US	Rating scale

The results of both studies using all four instruments are shown in Table 16. In both studies crude scores are presented for quartiles of function for each domain, as well as differences in scores adjusted for changes in other quality of life domains. The latter are more appropriate for use in the model to avoid overestimation of utility loss. Whilst Krahn *et al.* reports adjusted difference in utility between the highest and lowest quartile of function, Shimizu *et al.* reports the co-efficient for a unit increase in score. The adjusted ratio differences, shown in the table in italics, are based on the full score range of 0 to 100, and are likely to be an overestimate of the effect on utility, as demonstrated by the fact that they are less than the unadjusted values. Note also that Shimizu *et al.* includes a LUTS questionnaire score as well as the urinary function score in his statistical model, which is very likely to affect the urinary function co-efficient. Thus there are several disadvantages to the Shimizu *et al.* study, although the EQ-5D instrument was used. The Krahn *et al.* utility values derived using the HUI will be used as baseline in the model.

Table 16. Utility values for adverse effects of prostate cancer treatment

	Highest quartile	lowest quartile	difference	ratio low/high	adjusted difference[1]	ratio adjusted difference
Sexual dysfunction						
Krahn						
HUI	0.89	0.77	0.12	0.87	0.09	**0.90**
QWB	0.69	0.65	0.04	0.94	0.03	0.96
Shimizu						
EQ-5D	0.93	0.9	0.03	0.97	0.0000	1.00
SF36	0.76	0.73	0.03	0.96	0.0005	*0.93*
Urinary function						
Krahn						
HUI	0.85	0.76	0.09	0.89	0.05	**0.94**
QWB	0.71	0.57	0.14	0.80	0.11	0.85
Shimizu						
EQ-5D	0.94	0.84	0.1	0.89	0.0012	*0.87*
SF36	0.75	0.72	0.03	0.96	0.0003	*0.96*
Bowel function						
Krahn						
HUI	0.85	0.75	0.1	0.88	0.09	**0.89**
QWB	0.79	0.74	0.05	0.94	0.12	0.85
Shimizu						
EQ-5D	0.94	0.84	0.1	0.89	0.0014	*0.85*
SF36	0.75	0.71	0.04	0.95	0.0009	*0.88*

[1]Difference adjusted for other quality of life domains. Note the Shimizu values are per unit change in score on a range from 0 to 100.

Baseline age- related utility for men was taken from a study of the UK population, derived using the EQ-5D.[97] For men affected by adverse events the UK age-related baseline values were multiplied by the ratios of utility values for low/high function (final column of Table 16). The utility value of the hormone-refractory metastatic state was taken from Sullivan *et al.* (0.635).[96] The mean age of the population in the Sullivan *et al.* study was 72, at which age mean utility is 0.805. A ratio of 0.635/0.805= 0.79 was used for this state.

6.3 Mortality

The ERSPC trial reported a prostate cancer death rate ratio of 0.8 (CI 0.65 – 0.98) in the screening group compared to control, and an absolute risk difference of 0.71 deaths per thousand men.[1] Although of great clinical significance, this represents a very small absolute difference in survival. Estimation of survival by reading points from the published Nelson-Aalen curve at 11 years indicates prostate cancer survival in the screened cohort to be approximately 99.60% compared to 99.44% in the control cohort.[1] The curves do diverge further with time, but are heavily censored due to limited follow-up beyond this time, and therefore are unclear. From a modelling perspective this means that very small differences in mortality need to be estimated in order to look at the impact of different screening policies on prostate cancer survival.

The natural history model shows how screening impacts the numbers and stage of cancers detected, as well as PCa mortality. The PCa survival calibration is predicated on treatment patterns for the men in the ERSPC. In principle differences between treatment effectiveness could be incorporated into the model, but there is lack of such evidence. Although trials are currently underway (ProtecT[3], PIVOT[98]) there is currently no good RCT evidence comparing the principal treatment modes for localised cancers. The only such RCT compared radical prostatectomy with watchful waiting in the pre-PSA testing era.[99] In this trial 76% of cancers were T2, compared to 38% in the *control* arm of the ERSPC study.[1] Furthermore watchful waiting is not the most relevant comparison: otherwise healthy men may now be monitored and have radical treatment if the disease appears to be progressing. This latter option, active monitoring, is clearly of considerable interest in the context of screening, where many low stage, possibly indolent cancers are detected. The optimal frequency and content of monitoring, as well as the criteria for triggering reconsideration of radical treatment are however not well defined, and there is no

long term follow-up of patients on this regime.[25] In some studies of active monitoring up to 50% of men have had radical treatment within two years.[25]

The lack of direct RCT evidence between treatments is exacerbated by the common use of biochemical (PSA) progression as the study outcome measure, as several years follow-up is required to measure prostate cancer survival. A review identified 53 definitions of biochemical recurrence for patients having radical prostatectomy for localised cancer, and 99 for radiotherapy.[100] Varying definitions have a significant effect on results: a study reported biochemical survival to be 62% and 78% at five years for thresholds of 0.2 ng/ml and 0.5 ng/ml respectively.[101] Consensus definitions for biochemical failure following both radical prostatectomy and radiotherapy are now available and should reduce this problem in future, but differing PSA kinetics mean that the definitions for surgery and radiotherapy are not the same. Whilst PSA failure is associated with clinical failure and death[74] it is, even if consistently defined, not a surrogate for clinical progression or survival.[102] It is possible to model survival from PSA failure, but clearly uncertainty is introduced into the analysis.[93] However studies with prostate cancer mortality are predominantly from the pre-PSA era and their relevance to screened populations is more limited, both due to the differences in the cancers themselves, but also due to developments in treatment.

7. Results

7.1 Results overview

Four primary policy options have been investigated:

- Policy 1 - A single screen at age 50 years,
- Policy 2 – Screening every 4 years from age 50 to 74 years,
- Policy 3 – Screening every 2 years from age 50 to 74 years,
- Policy 4 – Screening every year from age 50 to 74 years.

The results for the primary policy options are presented in full in this chapter. In addition a range alternative screening programme designs have been investigated, the full results for which are presented in Appendix I to N. Probabilistic Sensitivity Analysis results on Policy 2 are reported in Appendix O.

The alternative screening programme designs investigated are:

- Single screen policies at ages 55, 60, 65, 70 years.
- Screening every 4 years from age 50 to 70, 55 to 74 and 55 to 70 years,
- Screening every 2 years from age 50 to 70, 55 to 74 and 55 to 70 years,

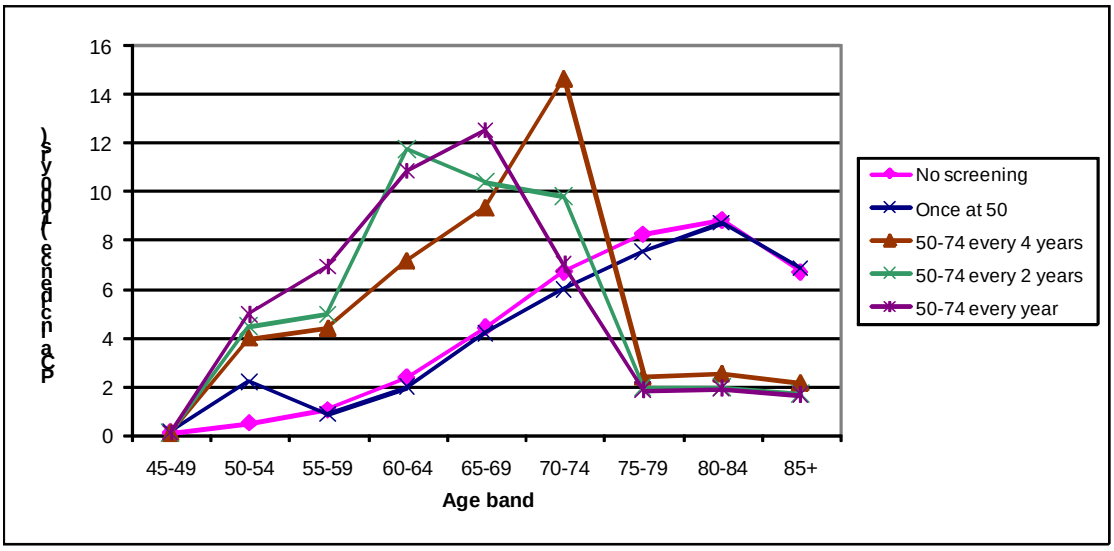
7.2 Screening policy results

Figure 6 gives the impact of screening on the age specific incidence of prostate cancer of the four primary screening options.

Table 17 presents the estimated impact of the primary screening policies on the identification and diagnosis of prostate cancer. Two key results emerge from an examination of the age specific cancer incidence figures presented in Figure 6:

- the policy of a single screen at age 50 has little impact on cancer incidence in the longer term,
- screening every year has little marginal impact on age specific incidence over and above two yearly screening.

Figure 6. Screening and the age specific incidence of PCa.



Overdiagnosis is defined as detection of prostate cancers in people who would otherwise have died of other causes without a symptomatic or clinical diagnosis of prostate cancer. Detection of potentially relevant cancers is defined as screen detection of cancers that would have been clinically diagnosed at some point in the future.

One of the benefits of the individual person level simulation approach is that these cases can be identified directly from the model and furthermore the lead time between screen detection and other cause death or clinical diagnosis can calculated are presented in the Table 17 below.

Table 17. Impact of screening on PCa identification

	Screening policies				
	No screening	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year
Lifetime probability of Pca	10.1%	10.2%	16%	16.5%	16.9%
Proportion of people screen detected with PCa who would have died of other causes (Overdetection)		18%	44%	45%	46%
Proportion of people screen detected who would have been diagnosed later with clinical PCa (Potentially relevant)		82%	56%	55%	54%
Mean lead time for PCs diagnosis in overdetected cases (yrs)		15.2	11.6	12.5	13.0
Mean lead time for PCa diagnosis in potentially relevant cases (yrs)		14.3	11.6	12.6	13.4

Figure 7 shows the probability distribution of lead time for potentially relevant cancers for each of the screening policies. The probability distribution of lead time for overdetected cancers is shown in Figure 8.

Figure 7. Lead time for potentially relevant cancers

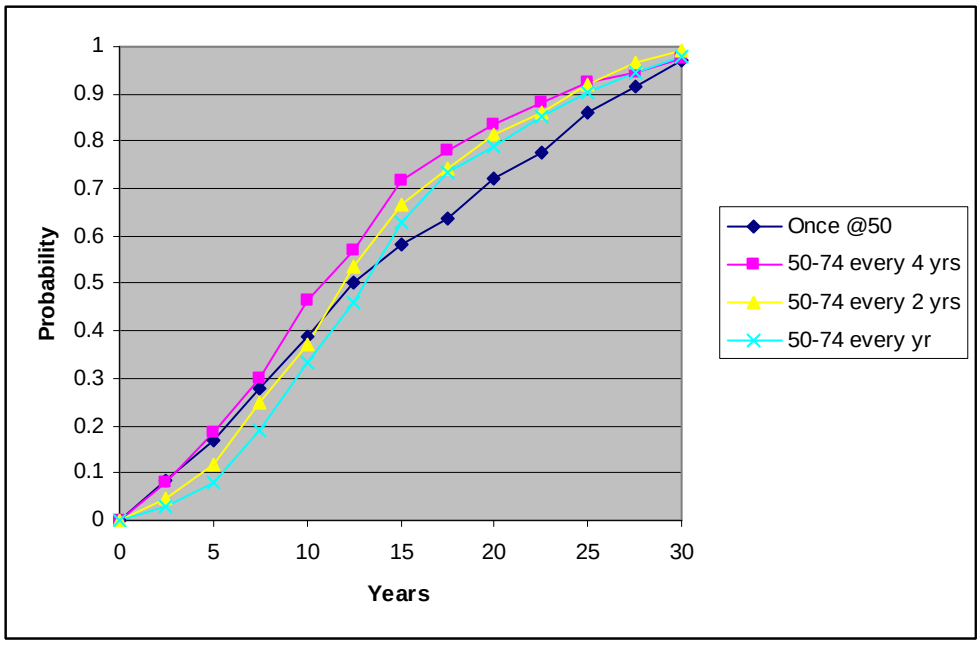


Figure 8. Lead time distribution for overdetected cancers

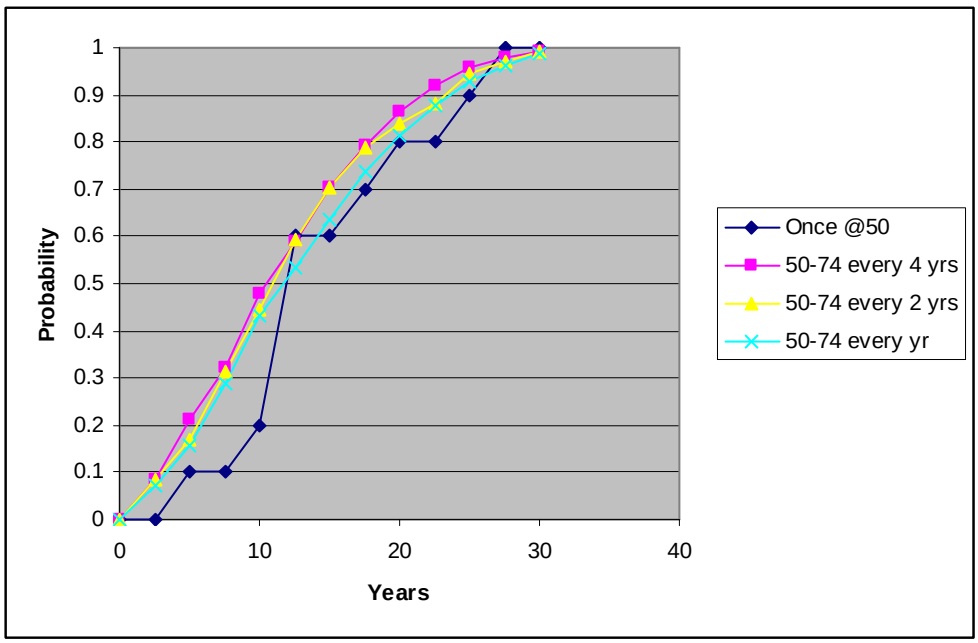


Table 18 presents the stage and grade distributions for screen detected PCa for a cohort of men aged 50 followed through for life.

Table 18. Stage and grade distribution for screen detected cancers

Once at 50	Local		Locally Advanced		Mets		Total	
G<7	1779.4	64.2%	93.4	3.4%	4.2	0.2%	1877.0	67.7%
G=7	407.7	14.7%	42.5	1.5%	0.0	0.0%	450.2	16.2%
G>7	394.9	14.2%	51.0	1.8%	0.0	0.0%	445.9	16.1%
Total	2582.0	93.1%	186.9	6.7%	4.2	0.2%	2773.1	100.0%
50-74 every 4 years	Local		Locally Advanced		Mets		Total	
G<7	35001.3	65.7%	1482.1	2.8%	0.0	0.0%	36483.4	68.5%
G=7	8026.3	15.1%	450.2	0.8%	0.0	0.0%	8476.4	15.9%
G>7	7737.5	14.5%	594.5	1.1%	0.0	0.0%	8332.0	15.6%
Total	50765.1	95.3%	2526.8	4.7%	0.0	0.0%	53291.9	100.0%
50-74 every 2 years	Local		Locally Advanced		Mets		Total	
G<7	40037.9	67.0%	573.3	1.0%	4.2	0.0%	40615.5	67.9%
G=7	9427.7	15.8%	182.6	0.3%	0.0	0.0%	9610.3	16.1%
G>7	9296.0	15.6%	254.8	0.4%	0.0	0.0%	9550.8	16.0%
Total	58761.6	98.3%	1010.7	1.7%	4.2	0.0%	59776.6	100.0%
50-74 every year	Local		Locally Advanced		Mets		Total	
G<7	42318.4	67.7%	186.9	0.3%	8.5	0.0%	42513.8	68.0%
G=7	9975.5	16.0%	72.2	0.1%	0.0	0.0%	10047.7	16.1%
G>7	9826.9	15.7%	123.2	0.2%	0.0	0.0%	9950.0	15.9%
Total	62120.8	99.4%	382.2	0.6%	8.5	0.0%	62511.5	100.0%

Table 19 presents the stage shift distribution for screen detected cancers that would otherwise have been diagnosed as clinical cancers. The figures in the tables are for a cohort of men aged 50 followed up through life. Thus for example a 2 yearly screening policy would be expected to identify 5614.1 potentially relevant cancers that would otherwise have arisen clinically as metastatic cancers.

Of these cancers that would have arisen as metastatic cancers, screening would detect 5117.3 as local cancers, 492.6 as locally advanced with only 4.2 cancers not achieving a stage shift and being detected as metastatic.

Table 19. Stage shift distribution for screen detected cancers that would otherwise be detected clinically

		Screen detected							
	Once at 50	Local		Locally Advanced		Mets		Total	
Clinical	Local	1295.2	100.0%					1295.2	100.0%
	LA	352.5	87.4%	51.0	12.6%			403.4	100.0%
	Mets	471.4	81.0%	106.2	18.2%	4.2	0.7%	581.8	100.0%
	Total	2119.1	92.9%	157.1	6.9%	4.2	0.2%	2280.5	100.0%

		Screen detected							
	50-74 every 4 years	Local		Locally Advanced		Mets		Total	
Clinical	Local	20613.5	100.0%					20613.5	100.0%
	LA	3044.9	84.7%	552.1	15.3%			3597.0	100.0%
	Mets	4382.6	79.8%	1108.4	20.2%	0.0		5491.0	100.0%
	Total	28041.0	94.4%	1660.5	5.6%	0.0		29701.4	100.0%

		Screen detected							
	50-74 every 2 years	Local		Locally Advanced		Mets		Total	
Clinical	Local	23518.2	100.0%					23518.2	100.0%
	LA	3427.1	93.4%	242.1	6.6%			3669.2	100.0%
	Mets	5117.3	91.1%	492.6	8.8%	4.2		5614.1	100.0%
	Total	32062.6	97.7%	734.7	2.2%	4.2		32801.5	100.0%

		Screen detected							
	50-74 every year	Local		Locally Advanced		Mets		Total	
Clinical	Local	24507.7	100.0%					24507.7	100.0%
	LA	3584.2	97.0%	110.4	3.0%			3694.6	100.0%
	Mets	5406.1	96.3%	199.6	3.6%	8.5	0.2%	5614.1	100.0%
	Total	33498.0	99.1%	310.0	0.9%	8.5	0.0%	33816.5	100.0%

Appendix I reports detailed estimates of the number of clinical cancers, screen detected cancers and incident cancers estimated under the different screening policies for a cohort of men aged 50 through to age 85+.

Figure 9 presents the age specific prostate cancer mortality achieved under the different screening options together with the results for no screening. It can be seen that despite the earlier detection of prostate cancer demonstrated for screening the consequent impact on prostate cancer mortality is estimated to be negligible for the one off screen at 50 and small for the repeat screening policies.

Figure 9. Age specific prostate cancer mortality

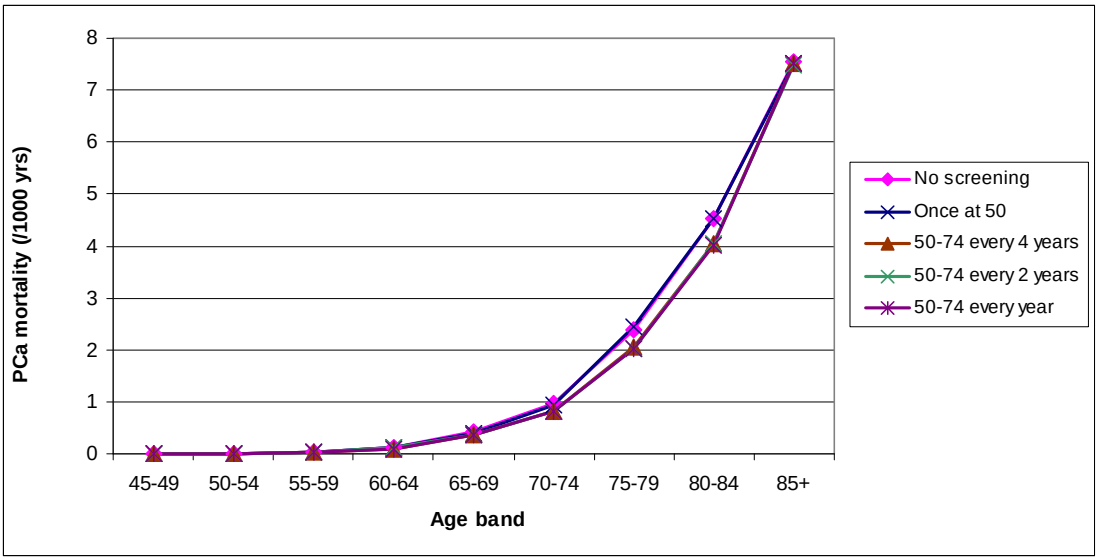


Table 20 shows the cumulative age band prostate cancer mortality rates for the different policies together with the relative rate of prostate cancer death for each of the policies compared to no screening. It should be noted that the estimated impact of screening on death rate ratio estimated by the model is in line with that demonstrated by the ERSPC trial. It is also noteworthy that the benefit in terms of relative rate of death for screening compared to no screening seems to attenuate as the older age bands are included in the analysis, that is with longer follow up. It is unclear whether this is an artefact of the structure of the model or whether this might be expected to be observed in practice.

Table 20. Prostate cancer mortality rates

	No screening	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year
	Cumulative age band mortality rate				
50-74	0.27	0.26	0.23	0.23	0.23
50+	1.12	1.11	1.01	1.01	1.01
	Relative rate of death				
50-74		0.96	0.84	0.84	0.84
50+		1.00	0.91	0.91	0.91

Table 21 presents the impact of screening on treatment duration and life years gained for screen detected potentially relevant cancers, that is cancers that are detected at screening and would otherwise have arisen as clinically detected cancers. For overdetected cancers, that is cancers that would otherwise have remained undetected at death from another cause, the average treatment duration is the lead time already presented in Table 14 and it is assumed that there is no survival gain associated with treatment. Table 17 presents the estimated duration of treatment for potentially relevant cancer under a policy of no screening and under each screening policy. The marginal treatment duration demonstrates that for potentially relevant cancers, screening results in earlier detection and longer exposure to treatment. The survival gain from treatment is estimated as the marginal treatment duration minus the estimated lead time in detection.

Table 21. Impact of screening on duration of PCa management and life years gained for potentially relevant cancers

	Screening policies			
	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year
Average treatment duration for screen detected potentially relevant cancers under a policy of no screening	11.5	8.7	9.0	9.2
Average treatment duration for screen detected potentially relevant cancers under screening	26.2	20.7	22.0	22.9
Average marginal treatment duration under screening	14.7	12.0	12.9	13.7
Average lead time	14.2	11.7	12.6	13.4
Average life years gained consequent on screening for potentially relevant cancers	0.5	0.3	0.3	0.3

Table 22 presents summary estimates of the impact of screening on duration of PCa management and life years gained for a cohort of men aged 50 for each potential screening programme followed up for life. It can be seen that for a policy of screening every four years between the age of 50 and 74 each person screened could expect to subsequently receive 0.86 years of management for a prostate cancer that would otherwise not have been diagnosed, 1.08 additional years of treatment for a potentially relevant cancer and could be expected to gain 0.03 years (10 days) of life from avoided or delayed prostate cancer mortality. This is equivalent to receiving on average 67 additional years of management for prostate cancer for each life year gained.

It is noteworthy that the policy of a single screen at age 50, the least effective policy from the point of view of the long term impact on overall population cancer incidence and mortality rates, is perhaps the best policy from the point of view of the individual with the lowest expected over-management and additional treatment for potentially relevant cancers. Thus cancers screen detected at age 50 would have a greater likelihood of arising clinically at some point in the future, there is thus a greater potential to benefit from screening, however these summary statistics do not account for the occurrence of adverse events associated with treatment and specifically do not account of the different marginal impact of adverse events associated with prostate cancer management in the younger age groups. These trade offs are explored further in the following chapter.

Table 22. Impact of screening on duration of PCa management and life years gained for a cohort of men aged 50

	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year
Total invited	401700	401700	401700	401700
Total screened at least once	320618	320618	320618	320618
Total overdetected cancers	493	23590	26975	28695
Total years of overmanagement in cohort	7473	274701	336621	373227
Expected years of overmanagement per person screened	0.023	0.857	1.050	1.164
Total potentially relevant cancers in cohort identified by screening	2280	29701	32802	33817
Total life yrs gained in cohort	1127	9268	9710	9890
Avg life yrs gained per person screened	0.0035	0.0289	0.0303	0.0308
Extra years Pca management in cohort	32581	345851	413233	452554
Average extra potentially relevant Pca management years per person screened	0.10	1.08	1.29	1.41
Average extra years of Pca management per life year gained	35.53	66.95	77.22	83.50

7.3 Impact of screening on treatment

Table 23 shows the distribution of initiation on to treatments by age for no screening. Note patients will progress to hormone therapy if they develop advanced disease, so some men will have more than one treatment. There is only limited activity data with which to compare these results. Prostatectomies are however routinely recorded for England and Wales in the Hospital Episode Statistics. For 2008/9 they show a total of 4026. Scaled to the population of UK men aged 50-74 gives 4550, so the model estimate of almost 3600 is slightly low. The proportion of men choosing different treatments by age and severity of cancer is taken from an analysis of BAUS data 2008.[75]. However, as the final column of the table shows, there are many men with localised cancers for whom treatment choice was not recorded. Some of these men may also have had surgery. Note no data was available to distinguish between active monitoring and watchful waiting, so the differentiation allocation between them by age is a model assumption.

Table 23. Initiation on to treatments by age - no screening

Age band	Radical prostatectomy	Radical radiotherapy	Radical radiotherapy & HT	Hormone Therapy	Active monitoring	Watchful waiting	Other local treatment
50 - 54	223	123	50	160	176	0	288
55 - 59	427	242	103	761	330	0	542
60 - 64	965	549	226	1640	760	0	1229
65 - 69	1518	888	316	3377	1253	0	1934
70 - 74	239	1016	442	6217	0	2909	2472
75 - 79	191	807	496	8128	0	2378	1992
80 - 84	3	23	25	7089	0	1402	1176
85 - 89	1	8	14	3945	0	473	385
Total	**3566**	**3656**	**1671**	**31318**	**2518**	**7163**	**10017**

Figures 10 to 14 show how the distribution of initiation on to the different principal treatments for prostate cancer varies according to screening policy.

Figure 10. Radical prostatectomy - distribution with time according to screening policy

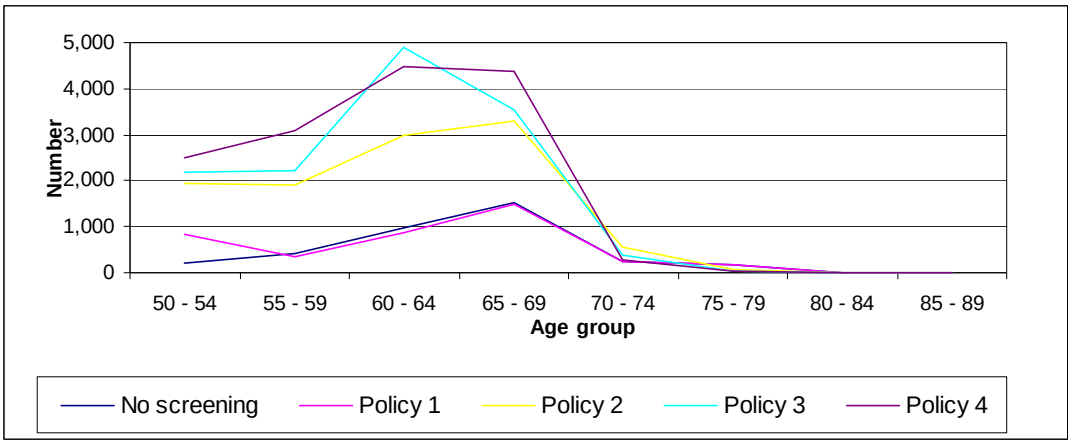


Figure 11. Radical radiotherapy - distribution with time according to screening policy

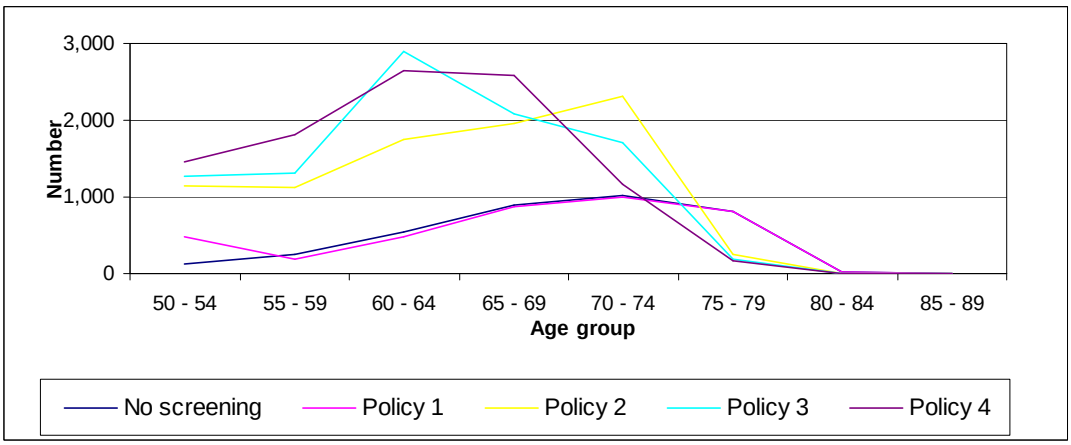


Figure 12. Radical radiotherapy with hormone therapy – distribution with time according to screening policy

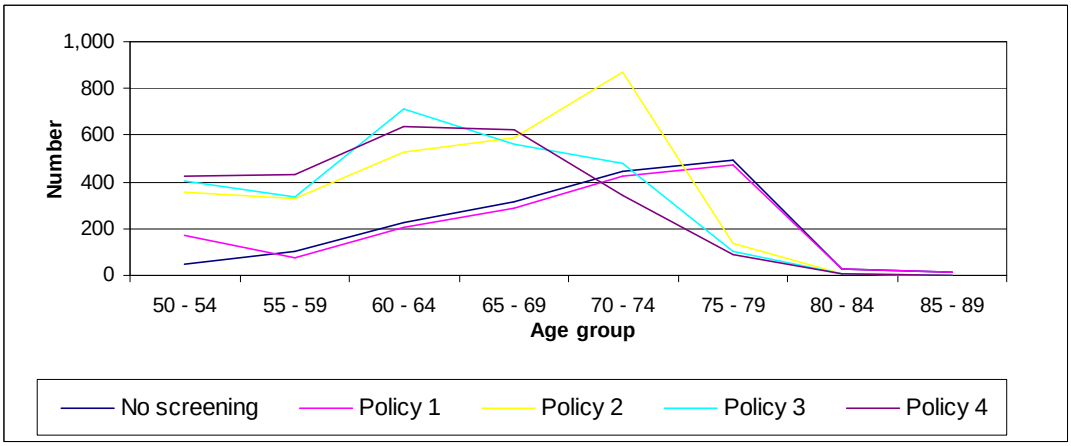


Figure 13. Active monitoring/Watchful waiting – distribution with time according to screening policy

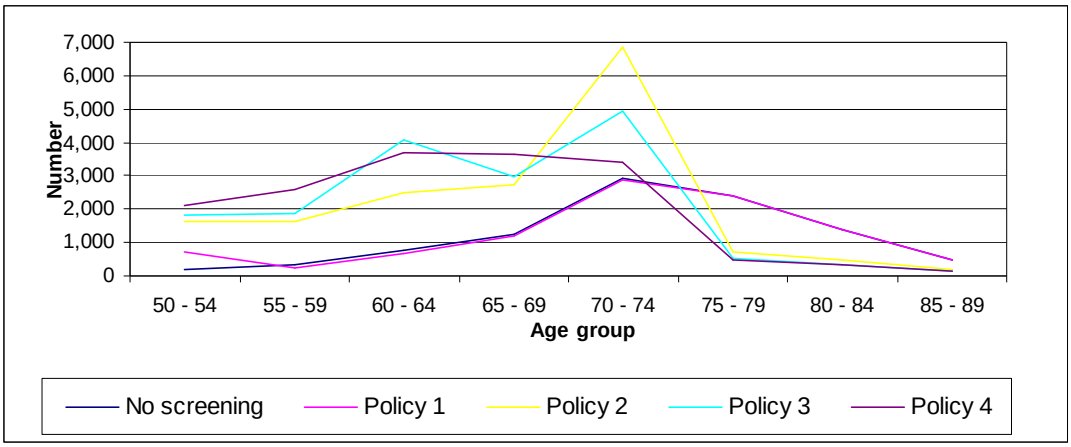
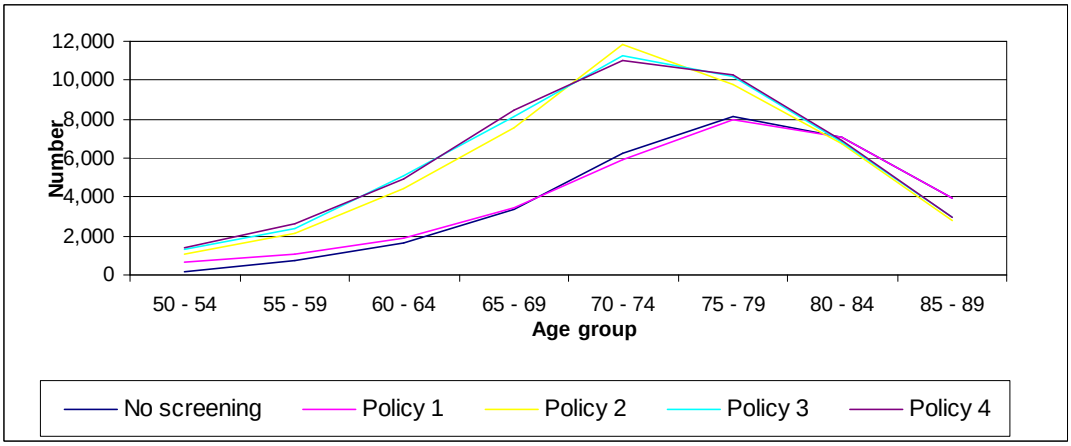


Figure 14. Hormone therapy - distribution with time according to screening policy



The analysis shows that screening once at age 50 (policy1) has little effect on treatment patterns apart from a small rise in radical treatment following the screen. The more frequent the screening (policies 1 through to 4), the more radical treatment in the screened age groups. Assuming treatment patterns remain constant radical treatment would increase by 2.5 – 3 times for repeat screening policies, primarily in men aged less than 75 years (Figures 10-12). Repeat screening also increases the number of men treated with hormone therapy at some time in their life, but by a much lesser extent: by approximately 50% more relative to current activity (Figure 14). Screening does reduce the number of men aged over 75 years starting therapy: radiotherapy, radiotherapy with neo-adjuvant hormone therapy, and watchful waiting

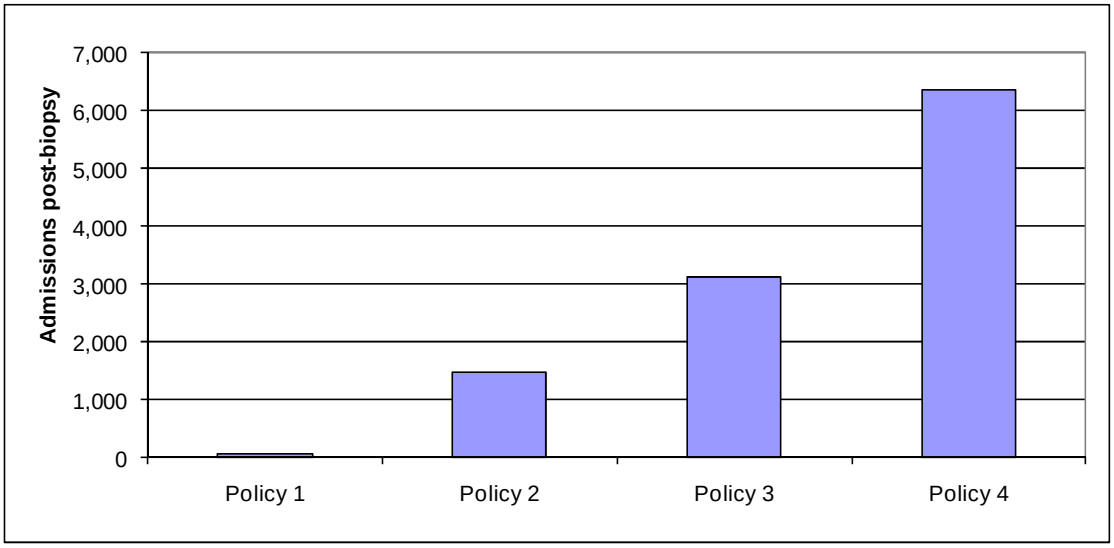
(Figures 11 - 13). The incremental total number of interventions compared to no screening for all screening policies are shown in Appendix J.

7.4 Impact of screening on adverse effects

Biopsy

Although the risk of infection requiring hospitalisation following biopsy is small (0.47%)[23] if a large number of men are biopsied as a result of screening the numbers of men admitted to hospital for infection will increase. Figure 15 shows the incremental number of admissions for infection in comparison to no screening.

Figure 15. Incremental hospital admissions for infection following biopsy in comparison to no screening



Screening once at 50 has a negligible effect, but annual screening increases the number of men affected by serious infection following biopsy by over 6000.

Mortality from radical prostatectomy

The risk of excess mortality from surgery is small, particularly for younger men. With no screening it is estimated that a total of 16 men will die as a result of surgery, rising to 57 with annual screening.

Long term adverse effects of treatment of prostate cancer

All interventional treatments for prostate cancer have adverse effects. Increasing the numbers of cancers detected through screening will result in more men suffering adverse effects of treatment, assuming treatment patterns for different age and disease stage remain the same. The model estimates the effect of different screening policies on the number of men affected by long term adverse effects of treatment for prostate cancer. Note that for the estimation of the adverse effects of treatment the men in the "other" (unknown) treatment category were allocated pro-rata to the other treatment categories for localised cancer.

Introducing screening and increasing the frequency results in increasingly more men being affected by long term adverse effects of treatment. The additional number of men affected by different adverse effects of treatment compared to no screening are shown in Table 24.

Table 24. Incremental (to no screening) number of men affected by adverse effects of treatment resulting from treatment for PCa

	Sexual dysfunction	Urinary incontinence	Bowel complications
Policy 1 :Once at age 50	3,406	71	34
Policy 2 : Every 4 years from 50 - 74	19,832	1,418	871
Policy 3 : Every 2 years from 50 - 74	23,273	1,867	989
Policy 4 : Every 4 years from 50 - 74	25,146	2,118	1,042

The results show an increase of up to 1000 men suffering from long term bowel complications resulting from radiotherapy. As baseline a rate of 10% was assumed, but the Smith study reports a rate of only 3.9%. With a rate of 3.9% the additional number of men with chronic bowel complications is 340 and 406 for policies 2 and 4 respectively.

Screening also results in an increase in urinary incontinence, from additional men treated with RP, but by far the most common adverse effect of treatment for prostate

cancer is sexual dysfunction. Regular screening with a frequency of one to four years would increase the number of men affected by between 20,000 and 25,000, depending on policy. However there is some uncertainty in these figures arising both from current treatment patterns (and also assumed future patterns), and dysfunction rates following treatment. Table 25 shows the results of a sensitivity analysis on key uncertain parameters driving the additional numbers of men affected by sexual dysfunction according to screening policy.

Table 25. Sensitivity analysis on key uncertain parameters driving the additional numbers of men affected by sexual dysfunction according to screening policy

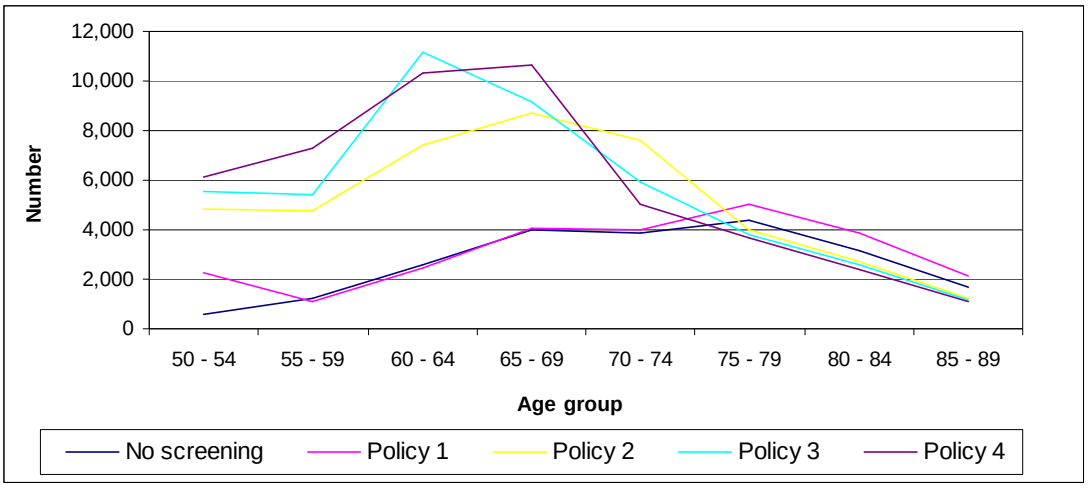
Analysis	Policy			
	1	2	3	4
1 Baseline	3,406	19,832	23,273	25,146
2 Local PC to HT as data	3,438	21,034	24,390	26,156
3 Unknown treatment assumed to be AM/WW	3,375	18,905	22,200	23,988
4 Incident rate of SD for AM/WW zero	3,342	18,550	21,410	22,876
5 Both 3 and 4	3,278	16,932	19,323	20,481

If men with local cancers with Gleason score <8 are given HT in the proportion currently suggested by activity data (analysis 2) instead of being assumed to have active monitoring or watchful waiting the numbers of men affected by SD rise slightly. If men with unknown treatment are assumed to have active monitoring or watchful waiting, to take in to consideration potential bias in recording interventions, rather than being allocated pro-rata to the other treatments as for baseline the rates for regular screening fall in the range 19,000 to 24,000 (analysis 3). The other key uncertain parameter is the rate of SD in men treated with AM or WW of 35%. It is not clear whether this is a real (possibly psychological effect) or a result of these patients progressing to hormone therapy. In a sensitivity analysis with the incident rate of SD for WW and AM set to zero of the number of men affected by SD from regular screening ranges between 18,500 and 23,000 (analysis 4). If the assumptions of analyses three and four are combined the additional numbers of men affected by SD

resulting from adverse effects of PCa treatment fall in the range 17,000 to 20,500 for regular screening policies.

As well as affecting the overall incidence of adverse effects, screening policy also affects the age at which they occur. If men are treated at a younger age for PCa as a result of screening they will also incur adverse effects earlier, and have to live with them longer, as illustrated by Figure 16 for sexual dysfunction.

Figure 16. Incidence of sexual dysfunction with time



Tables showing the number of men affected by adverse effects of diagnosis and treatment for prostate cancer for all screening policies are shown in Appendix K. Note the long term adverse effects of hormone treatment which include increased risk of fractures and cardiovascular mortality have not been included.

7.5 Impact of screening on QALYs

QALYs allow differences in quality of life to be taken into consideration as well as differences in survival. Table 26 shows the effect of different screening policies on incremental QALYs compared to baseline. The ratios per man with cancer are on all men who develop cancer, whether detected during their lifetime or not, so the denominator is the same for all policies. It shows that all screening policies result in loss in QALYs, with greater loss the more frequent the screen. The loss in QALYs

reflects the effects of adverse effects of treatment. Note only chronic adverse effects are considered in the model. Acute effects will be experienced by more men, but being by definition of short duration will have little effect on overall QALYs.

Table 26. Impact of screening policies on quality adjusted life years

Policy	QALYS	Discounted QALYs	QALYS/per man with cancer	Discounted QALYs per man with cancer
Policy 1 :Once at age 50	-2,915	-2,149	-0.035	-0.026
Policy 2 : Every 4 years from 50 - 74	-89,906	-50,154	-1.09	-0.61
Policy 3 : Every 2 years from 50 - 74	-105,282	-58,805	-1.28	-0.71
Policy 4 : Every year from 50 - 74	-113,266	-63,389	-1.37	-0.77

As sexual dysfunction is the most common adverse effect of PCa treatment its incidence, and the utility loss attached to it, will be key parameters in determining incremental QALYs for different screening policies. The model has been careful not to overestimate the effects of PCa treatments on SD, by explicitly taking into account underlying SD in the male population, both in the incidence resulting from treatment, but also in the proportion of men that would have been affected in due course with increasing age. Tables 27 and 28 show sensitivity analyses addressing uncertainty in parameters associated with SD. Note the scenarios in Table 27 are the same as those in Table 25.

Table 27. Sensitivity analysis on factors affecting the incidence of sexual dysfunction on incremental discounted QALYs

	Policy			
Analysis	1	2	3	4
1 Baseline	-0.026	-0.608	-0.713	-0.768
2 Local PC to HT as data	-0.027	-0.623	-0.730	-0.787
3 Unknown treatment assumed to be AM/WW	-0.024	-0.592	-0.693	-0.745
4 Incident rate of SD for AM/WW zero	-0.024	-0.588	-0.685	-0.735
5 Both 3 and 4	-0.020	-0.562	-0.650	-0.694

Table 28. The effect of the utility value of sexual dysfunction on incremental QALYs

Ratio utility SD/healthy	0.9 (baseline)		0.95		1.00	
Policy	QALYS/per man with cancer	Discounted QALYs per man with cancer	QALYS/per man with cancer	Discounted QALYs per man with cancer	QALYS/per man with cancer	Discounted QALYs per man with cancer
Policy 1 :Once at age 50	-0.035	-0.026	-0.026	-0.020	-0.011	-0.010
Policy 2 : Every 4 years from 50 - 74	-1.09	-0.61	-1.03	-0.58	-0.89	-0.50
Policy 3 : Every 2 years from 50 - 74	-1.28	-0.71	-1.20	-0.68	-1.02	-0.58
Policy 4 : Every year from 50 - 74	-1.37	-0.77	-1.29	-0.73	-1.09	-0.62

Both analyses show negative QALYs for all scenarios. Even if it assumed that SD has no effect on utility the QALYs remain negative due to the other adverse effects of treatment. A further sensitivity analysis was done to test the effect of the natural history model output showing more men in the unscreened group having their PCa detected at death. In the baseline impact model these men do not suffer any QALY loss from hormone refractory metastatic cancer. This assumption was modified so that all men dying of PCa in the metastatic disease state were assumed to suffer the QALY loss associated with HR cancer. In fact this has a negligible effect on the incremental QALYs: for Policy 4 with the greatest loss the difference is in incremental discounted QALYs is 0.004, or 0.5%.

The incremental QALYs for all screening policies compared to no screening are shown in Appendix L. It shows that incremental QALYs for screening compared to no screening are negative for all screening policies, and that the more frequent the screening, the greater the harm.

7.6 Impact of screening on resources

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The estimated incremental demand for different items of resource for the baseline screening policies

compared to no screening are in Table 29. Tables for all screening policies are in Appendix M. The latter tables also differentiate between resources required for screening and diagnosis and those required for treatment and monitoring of men with PCa. Note the figures show incremental resource use with time for a cohort of men aged 50. If an ongoing screening programme were introduced, once fully implemented the total additional resources required each year for the entire population of men aged over 50 could be approximated by the lifetime totals for men aged 50 (assuming the population distribution by age remains constant).

Table 29. Total incremental resource use by screening policy compared to no screening

	Policy			
Resource item	**1**	**2**	**3**	**4**
General Practice Nurse	336,430	2,481,959	4,068,071	7,142,204
PSA test	356,849	2,749,881	5,605,976	9,893,161
GP appointment	-27,111	-74,233	35,512	380,231
Biopsy	16,470	314,910	670,195	1,368,530
Hospital admission (post biopsy)	77	1,465	3,119	6,369
Bone scan	1,528	21,995	24,997	25,871
CT scan	1,528	23,541	27,409	28,437
MRI scan	0	-1,546	-2,413	-2,566
Outpatient attendance	136,456	2,010,848	2,946,401	4,245,141
RP	377	7,180	9,727	11,171
RT planning	219	6,025	6,726	7,073
RT fractions	8,106	222,917	248,854	261,701
HT (annual)	20,503	247,793	272,359	280,649
Dexa scan	10,240	123,645	135,882	140,010
Hormone refractory treatment	555	2,804	2,836	2,804
Terminal care	8	-951	-1,011	-1,045
Other treatment for local PC	465	9,783	11,365	11,975

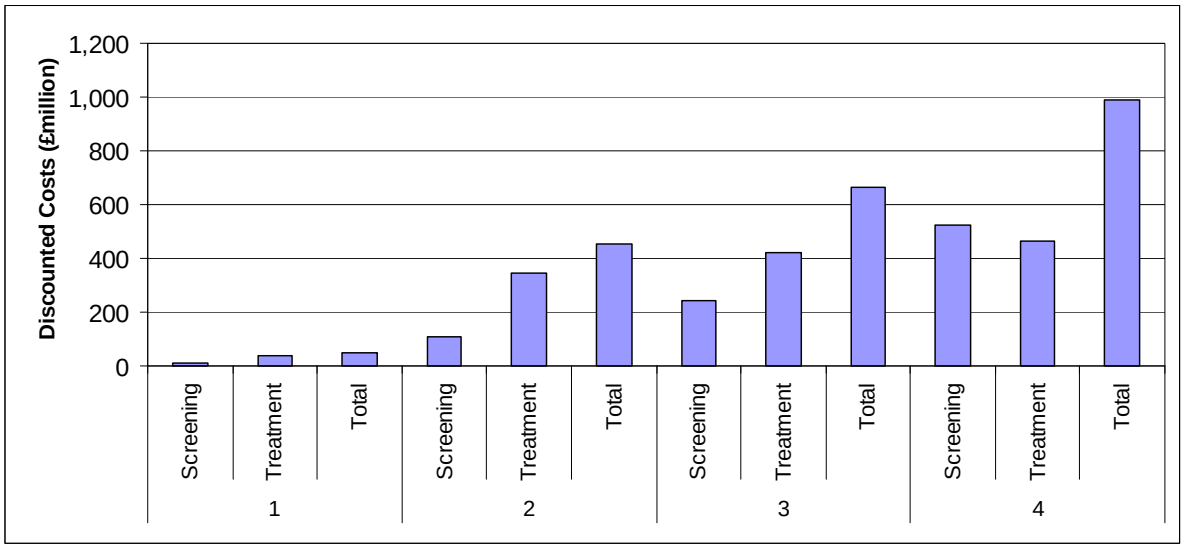
As would be expected the largest increase in resources required would be those associated with screening and diagnosis: policy 4 (annual screening) would result in almost 10 million more PSA tests per year and 1.4 million biopsies. The change in requirement for some resources is partially dependent on the assumptions made regarding the implementation of screening: for example it has been assumed that GP practice nurses would be responsible for taking the blood sample for a PSA test, and would give men on HT their regular injections. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, outpatient appointments) there would be some small savings in others relating to the diagnosis of more advanced disease such as bone and MRI scans. Some reduction in the need for hormone treatment might be anticipated from screening if earlier detection and treatment of disease results in delayed progression to advanced disease. In fact, whilst the natural history model predicts that there will be some delay in patients who are diagnosed with local disease reaching advanced disease as a result of screening, this is more than offset by the earlier detection of men with advanced disease, resulting overall in more years of hormone treatment for the cohort.

Note the increase in demand for treatment for hormone refractory disease resulting from screening reflects the natural history model prediction of more cancers being detected at death with no screening. If the proportion requiring treatment for HR disease is in fact proportionate to the number of prostate cancer deaths, there would be a reduction in need for the treatment of hormone refractory disease resulting from screening.

7.7 Impact of screening on costs

Figure 17 shows the total discounted screening and treatment costs for screening policies 1 to 4 compared to no screening. Screening costs also include diagnostic tests, and treatment costs include monitoring of patients with PCa. Costs are discounted to age 50. Note these costs do not include the costs of administering a screening programme.

Figure 17. Total discounted screening and treatment costs for screening policies 1 to 4 compared to no screening



The total additional discounted costs of a screen once policy at 50 are £50 million, rising to almost £1 billion for an annual screening policy. The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men screened falls. With an annual screening policy (4) the costs of screening are greater than those for treatment. However the screening costs are likely to be slightly overestimated for the more frequent screening policies as the number of men screened is not adjusted for the number of men without diagnosed cancers who are monitored.

Table 30 shows how the incremental costs are comprised.

Table 30. Incremental costs by screening policy and resource item (£million)

	Policy			
Resource item	**1**	**2**	**3**	**4**
General Practice Nurse	4.0	29.7	48.6	85.0
PSA test	2.4	13.9	29.4	62.5
GP appointment	-1.0	-2.9	1.4	14.7
Biopsy	5.1	96.8	206.0	420.7
Hospital post biopsy	0.2	3.6	7.6	15.6
Bone scan	0.3	3.8	4.3	4.5
CT scan	0.2	2.7	3.1	3.3
MRI scan	0.0	-0.3	-0.5	-0.5
Outpatient attendance	18.9	279.0	408.0	585.9
Radical prostatectomy	2.5	48.0	64.9	74.6
Radiotherapy planning	0.2	4.2	4.8	5.0
Radiotherapy fractions	1.7	42.6	48.4	51.0
HT (annual)	22.6	274.7	304.4	315.3
Dexa scan	0.8	9.9	10.9	11.3
HR treatment	4.4	22.2	22.4	22.2
Terminal care	0.0	-4.1	-4.4	-4.5
Total Cost (£million)	**62.1**	**823.8**	**1,159.5**	**1,666.4**
Discounted cost (£million)	**49.0**	**455.3**	**665.1**	**987.9**

The proportion of the total cost comprised by each resource item varies slightly between policies. Biopsy costs in particular vary from 8% of the total cost for Policy 1 to 25% for Policy 4. For all policies outpatient attendances and hormone treatment are the two largest cost elements, varying between 30-35% and 19-36% of the total costs respectively. Note the additional costs for hormone refractory care comprise 7% of the undiscounted costs for Policy 1, and 1.3% for Policy 4. However, as they occur at the end of life they will comprise a smaller proportion of the total discounted costs. The tables in Appendix N show the costs for all the screening policies.

8. Conclusions and discussion

8.1 Summary of main results

Detection, stage distribution, survival and overall prostate cancer management duration.

A one off screen at age 50 years is estimated to have minimal impact the longer term incidence of PCa. However, more intensive policies can be effective in the early identification cancer, with four yearly and two yearly policies increasing the lifetime risk of PCa from around 10% under no screening to 13%. A small marginal increase in PCa identification is obtained by moving to an annual policy.

Overdetection has been defined as the detection of cancers in individuals who would otherwise have died of natural causes without a clinical diagnosis of PCa. All the repeat screening policies are estimated to entail approximately 45% overdetection of PCa, these cases are estimated to be exposed to an average of 11-13 years of management for their PCa. Whilst the single screen policy has a lower rate of cancer detection, the overdetection rate is also reduced at around 18%, however these cases experience over 15 years of overmanagement.

Potentially relevant cancers are defined as screen detected cancers that would otherwise arise clinically at a later date. The estimated mean lead time for potentially relevant cancers is approximately 11-15 years. This early detection is estimated to lead to a stage shift in cancers, with 85% of locally advanced and 80% of metastatic cancers being screen detected at the local stage with a 4 year screening policy.

The repeat screen policies are associated with an expected life years gained of approximately 0.03 years (10-11 days) for each individual accepting screening, with an equivalent figure of 0.004 (1.2 days) for the single screen policy. Whilst screening policies can often be associated with small expected gains for each individual,

prostate cancer screening is also associated with a high level of disease management, for instance for each life year gained the repeat screen policies are associated with approximately 67-84 years of additional prostate cancer management and 36 years for the single screen policy.

The single screen at 50 policy is estimated to have a minimal impact on overall prostate cancer incidence and mortality rates, being the least effective policy in terms of relative rate of prostate cancer mortality, 0.96 as compared to 0.84 for the repeat screen policies. However, it might be considered the most attractive policy from the individual perspective as it entails the least expected excess prostate management to obtain one additional life year gained.

Treatment

The analysis shows that screening once at age 50 (policy1) has little effect on current treatment patterns apart from a small rise in radical treatment following the screen. Radical treatment in the screened age groups increases with screening intensity. Assuming treatment patterns remain constant radical treatment would increase by 2.5 – 3 times for repeat screening policies, primarily in men aged less than 75 years. Repeat screening also increases the number of men treated with hormone therapy at some time in their life, but by a much lesser extent: by approximately 50% more relative to current activity.

Adverse effects of diagnosis and treatment

Adverse effects of the PSA test are rare and mild. Serious adverse effects of biopsy are infrequent, but nevertheless a small proportion of men (0.47%) will be hospitalized for infection resulting from biopsy. This will result in an additional 1500 men being affected for a four yearly screening policy.

The incidence of long term adverse effects of treatment increases with screening intensity. For example the additional number of men affected by urinary incontinence compared to no screening varies from 1400 for policy 2 and over 2000 for policy 4. Similarly there is up to an additional 1000 men suffering from long term bowel complications resulting from radiotherapy. By far the most common adverse effect of treatment for prostate cancer is sexual dysfunction. Regular screening with a frequency of one to four years would increase the number of men affected by between 20,000 and 25,000, depending on policy. There is some uncertainty in these figures arising both from current treatment patterns (and also assumed future patterns), and dysfunction rates following treatment, but sensitivity analysis shows that even with more favourable assumptions at least 16,000 men would be affected with regular screening. Note the model has been careful not to overestimate the effects of PCa treatments on SD, by explicitly taking into account underlying SD in the male population, both in the incidence resulting from treatment, but also in the proportion of men that would have been affected in due course with increasing age. Screening policy also affects the age at which adverse events occur. If men are treated at a younger age for PCa as a result of screening they will also incur adverse effects earlier, and have to live with them longer.

QALYs (Quality adjusted life years)

QALYs allow differences in quality of life to be taken into consideration as well as differences in survival. All screening policies result in loss in QALYs: for repeat screening the loss ranges from 1.1 to 1.4 QALYs undiscounted, or 0.3 to 0.8 discounted QALYs, per man with prostate cancer (detected or not). The more frequent the screening, the greater the QALY loss. The loss in QALYs reflects the adverse effects of treatment. As sexual dysfunction is the most common adverse effect of PCa treatment its incidence, and the utility loss attached to it, are key parameters in determining incremental QALYs for different screening policies.

Sensitivity analysis showed that QALYs remained negative for all of the baseline screening policies when varying these parameters.

Resources

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The resources most impacted are those required for screening itself. Policy 4 (annual screening) would result in almost 10 million more PSA tests per year and 1.4 million biopsies. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, hormone treatment, outpatient appointments) there would be some small savings in others relating to the diagnosis of more advanced disease such as bone and MRI scans.

Costs

The total additional lifetime discounted costs for a cohort of men aged 50 of a screen once policy at 50 are £50 million, rising to almost £1 billion for an annual screening policy. Note costs are discounted to age 50 for all policies and **do not include the costs of administering a screening programme.** The actual annual cost of screening is £0.6 to £1.7 billion per year. The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men screened falls. With an annual screening policy the costs of screening are greater than those for treatment. The proportion of the total cost comprised by each resource item varies slightly between policies. Biopsy costs in particular vary from 8% of the total cost for Policy 1 (single screen at 50) to 25% for Policy 4 (annual screening). For all policies outpatient attendances and hormone treatment are the two largest cost elements, varying between 30-35% and 19-36% of the total costs respectively.

8.2 Discussion

A model of the natural history of PCa has been developed and calibrated to a UK population. The output from this model has been validated against other UK registry data and provides results for a 4 year screening policy that are in line with results from the Rotterdam section of the ERSPC. There is thus a reasonable basis for estimating the impact of screening on the identification and diagnosis of PCa in the UK. However predicting the impact of these changes in the pattern of treatment and survival is difficult for some of the reasons discussed below.

Prediction of changes in treatment patterns resulting from different screening policies is uncertain due both to possible changes in treatment patterns arising from screening (identifying a higher proportion of very low risk tumours) and an uncertain current baseline due to the limited quality of current data. Data from the cancer registries does not record men who have active monitoring or watchful waiting, which are recommended options for men with less aggressive localised cancers. Age, stage, Gleason score and treatment information was poor with just 33% of patients having complete data. Treatment data from BAUS was used in the model. Although relying on voluntary submissions from consultant urologists, and therefore from only a (potentially biased) subset of patients, active monitoring is recorded. 75% of patients had treatment recorded, and approximately 50% had complete age, stage, Gleason score and treatment information. Possible biases in the recording of treatment, likely in favour of active treatments and RP in particular, mean that percentages of men having each treatment calculated on the population of men with known treatment may overestimate active treatment. The alternative scenario of assuming all men with no recorded treatment are on AM or WW was explored in sensitivity analysis.

Screening will identify a greater proportion of low risk cancers which potentially may be managed with active monitoring, as indicated in the NICE guideline.[7] The recommendation that low risk cancers be managed in this way has, however proved controversial. The frequency of monitoring required, the tests that should be performed routinely and the criteria that should initiate consideration of radical treatment are also poorly defined.[25] The NICE prostate cancer guideline merely recommends that men should have at least one further biopsy.[7] Men need confidence in this form of management or they will choose radical therapy within a short period of time anyway – up to 50% within two years,[25] although other studies have reported much lower rates: 79% actuarial freedom from treatment at five years.[26]

Published rates of adverse effects of treatment vary widely, and are dependent on many factors including how the adverse events are measured, the time from treatment, and differences in interventional technique. They may also be confounded by baseline malfunction, particularly sexual function, and decline in function with age. Two large population studies, one from the US[29;82], the other from Australia[84], addressed some of these issues, measuring chronic effects with the same measurement instruments across different treatments, and adjusting for baseline malfunction. The results of the more recent of these (Smith)[84] were generally used in the model.

Whilst the death rate ratio in the ERSPC trial of screening every 4 years (0.8) was statistically significant[1], this represents an estimated difference in prostate cancer survival of only approximately 0.16% at 11 years (99.60% compared to 99.44%). Despite the size of the trial the 95% confidence interval for the death rate ratio is 0.65 to 0.98. An analysis adjusting for non-attendance and contamination (previous PSA testing) estimates the screening effect on death rate ratio to be somewhat greater at

approximately 0.7 (95% CI 0.51-0.93)[30]. The effect on PCa survival between screened and unscreened cohorts remains small.

From the perspective of a cost utility analysis no overall survival benefit was found from screening, so any differences in QALYs (quality adjusted life years) between screening and no screening are derived solely from shifts between disease states (undetected, localised and advanced disease, resulting either from earlier detection or effective treatment), the proportions of men affected by adverse effects of treatment and the utility values for those states. Some reduction in the need for treatment for advanced disease might be anticipated from screening if earlier detection and treatment of disease results in delayed progression to advanced disease. In fact, whilst the natural history model predicts that there will be some delay in patients who are diagnosed with local PCa reaching advanced disease as a result of screening, this is more than offset by the earlier detection of men with advanced disease, resulting overall in more years of treatment of advanced disease for the cohort. This effect, combined with the predicted increase in radical treatment due to screening, with its associated adverse effects, results in the incremental QALYs for all screening policies being negative compared to no screening. The more frequent the screening the more QALYs lost.

The model also illustrates the increase in resources that would be required to implement a prostate screening programme. These would be significant, particularly for those associated with screening itself. A screening test with higher specificity would reduce the number of biopsies required. An analysis of patients recruited to the ProtecT trial shows that specificity may be improved by a second PSA test in selected men. The authors estimate that 61% of men would require a second test, avoiding one biopsy for every five repeated PSA tests.[103] Such a strategy would be cost saving, but compliance may be an issue.

A proportion (~20% for Policy 2) of the considerable increase in requirement for outpatient attendances resulting from screening arises from the assumption that men with a raised PSA test but negative biopsy will be monitored on an outpatient basis. This is approximately 7% of men screened.[67] It has been assumed these men will on average be seen three times and have one further biopsy. There appears to be variation in clinical practice, and this assumption may overestimate the resource consequences. However, if a screening programme were to be introduced a strategy for the management of these men would need to be in place.

Another study estimating the costs of introducing a screening programme in the UK based on the ERSPC study concluded the additional cost would be €61 million, or approximately £55 million assuming an exchange rate of €1.12 to a pound sterling.[104] This cost is considerably lower than the results of this study suggests. Heijnsdijk *et al.*[104] uses costs from Dutch sources, and whilst the costs for PSA screening are similar in both studies, the cost of biopsy used by Heijnsdijk *et al.*[104] is much lower; €92 compared to £307. Another difference is there appears to be no consideration of patient monitoring, either for those declining biopsy or for those who have a positive PSA test but are biopsy negative. As discussed above the latter in particular has a significant impact on resource use.

Implications for screening policy in the UK

The degree of contamination in the PLCO study is the most plausible explanation of its failure to find any significant difference in prostate cancer death rates between the screened and unscreened cohorts. Its results suggest that beyond a certain level there is no further benefit from more frequent screening.

The results of the ERSPC therefore are more representative of the benefits of screening. There was a significant reduction in prostate cancer death rate ratio of 0.8 (95% CI 0.65, 0.98).[1] The ERSPC study was also affected by contamination and non-

compliance. Adjustment for these suggest a reduction in prostate cancer death rate ratio of 0.7 (95% CI 0.51, 0.93).[30] Clearly in practice though there will be a degree of contamination and non-compliance also. There was no difference in overall survival.

The model shows that a single screen at age 50 has little effect on age specific incidence of PCa. Similarly a policy of annual screening has only a small marginal effect compared to screening every two years.

Assuming treatment patterns remain constant radical treatment would increase by 2.5 – 3 times for a repeat screening policy, primarily in men aged less than 75 years. The incidence of long term adverse effects of treatment (urinary symptoms, bowel function, sexual dysfunction) would rise accordingly, and shifts the incidence to younger age groups, hence increasing prevalence.

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The resources most impacted are those required for screening itself. Policy 4 (annual screening) would result in almost 10 million more PSA tests per year and 1.4 million biopsies. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, hormone treatment, outpatient appointments) there would be some small savings in others relating to the diagnosis of more advanced disease such as bone and MRI scans.

The total additional discounted costs of a screen once policy at 50 are £50 million, rising to almost £1 billion for an annual screening policy. Note costs are discounted to age 50 for all policies and **do not include the costs of administering a screening programme.** The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men screened

falls. With an annual screening policy (4) the costs of screening are greater than those for treatment.

A proportion of the additional outpatient attendances arising from screening are for the monitoring of men who have raised PSA but negative biopsy. Clinical practice varies and the model may overestimate the resources required. However since this group comprises approximately 7% of all men screened, if screening for prostate cancer were to be introduced a strategy for managing these men would need to be in place.

9. References

(1) Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V et al. Screening and prostate-cancer mortality in a radomized European study. *New England Journal of Medicine* 2009; 360(13):1320-1328.

(2) Andriole GL, Grubb RL, III, Buys SS, Chia D, Church TR, Fouad MN et al. Mortality results from a randomized prostate-cancer screening trial. *New England Journal of Medicine* 2009; 360(13):1310-1319.

(3) Donovan.J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L et al. Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. *Health Technol Assess* 2003; 7(14):1-49.

(4) Cancer Research UK. CancerHelp UK [2009 [cited 2009 July 6]; Available from: URL:http://www.cancerhelp.org.uk/

(5) Office for National Statistics. ONS [2009 Available from: URL:http://www.statistics.gov.uk/

(6) Cancer Research UK. CancerStats key facts on prostate cancer. Cancer Research UK [2009 Available from: URL:http://info.cancerresearchuk.org/cancerstats/types/prostate/

(7) National Institute for Health and Clinical Excellence (NICE). Prostate cancer: diagnosis and treatment: full guideline. 2008. National Collaborating Centre for Cancer.

(8) Selley S, Donovan J, Faulkner A, Coast J, Gillatt D. Diagnosis, management and screening of early localised prostate cancer. *Health Technol Assess* 1997; 1(2):i-96.

(9) Burford DC, Kirby M, Austoker J. Prostate Cancer Risk Management Programme: information for primary care - PSA testing in asymptomatic men. 2009. NHS Cancer Screening Programmes.

(10) American Urological Assoication. The management of localized prostate cancer: patient guide. http://www auanet org/content/guidelines-and-quality-care/clinical-guidelines/patient-guides/pc08 pdf [2008

(11) Ben-Shlomo Y, Evans S, Ibrahim F, Patel B, Anson K, Chinegwundoh F et al. The risk of prostate cancer amongst Black men in the United Kingdom: The PROCESS cohort study. *European urology* 2008; 53(1):99-105.

(12) Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. *J Natl Cancer Inst* 2000; 92(1):61-68.

(13) Lawson KA, Wright ME, Subar A, Mouw T, Hollenbeck A, Schatzkin A et al. Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. *JNCI Journal of the National Cancer Institute* 2007; 99(10):754.

(14) John EM, Schwartz GG, Koo J, Van Den Berg D, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Research* 2005; 65(12):5470-5479.

(15) John EM, Dreon DM, Koo J, Schwartz GG. Residential sunlight exposure is associated with a decreased risk of prostate cancer. *Journal of Steroid Biochemistry and Molecular Biology* 2004; 89:549-552.

(16) Gulden JWJ, Kolk JJ, Verbeek ALM. Work environment and prostate cancer risk. 1995.

(17) Matzkin H, Soloway MS. Cigarette smoking: a review of possible associations with benign prostatic hyperplasia and prostate cancer. *Prostate* 1993; 22(4):277-290.

(18) Le Marchand L, Kolonel LN, Yoshizawa CN. Lifetime occupational physical activity and prostate cancer risk. *American journal of epidemiology* 1991; 133(2):103-111.

(19) Sarma AV, McLaughlin JC, Wallner LP, Dunn RL, Cooney KA, Schottenfeld D et al. Sexual behavior, sexually transmitted diseases and prostatitis: the risk of prostate cancer in black men. *J Urol* 2006; 176(3):1108-1113.

(20) Rosenblatt KA, Wicklund KG, Stanford JL. Sexual factors and the risk of prostate cancer. *American journal of epidemiology* 2001; 153(12):1152-1158.

(21) Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine.[erratum appears in Clin Chem 1993 Aug;39(8):1589]. [Review] [77 refs]. *Clin Chem* 1993; 39(4):561-577.

(22) Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol* 2006; 175(5):1605-1612.

(23) Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schroder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology* 2002; 60(5):826-830.

(24) Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A et al. Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review. *Health Technol Assess* 2009; 13(5):iii-xiii.

(25) Martin RM, Gunnell D, Hamdy F, Neal D, Lane A, Donovan J. Continuing Controversy Over Monitoring Men With Localized Prostate Cancer: A Systematic Review of Programs in the Prostate Specific Antigen Era. *The Journal of Urology* 2006; 176:439-449.

(26) Hardie C, Parker C, Norman A, Eeles R, Horwich A, Huddart R et al. Early outcomes of active surveillance for localized prostate cancer. *BJU Int* 2005; 95:956-960.

(27) Hummel S, Paisley S, Morgan A, Currie E, Brewer N. Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review. *Health Technol Assess* 2003; 7(33):1-157.

(28) Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med* 2008; 148(6):435-448.

(29) Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst* 2004; 96(18):1358-1367.

(30) Roobol MJ, Kerkhof M, Schr÷der FH, Cuzick J, Sasieni P, Hakama M et al. Prostate Cancer Mortality Reduction by Prostate-Specific AntigenûBased Screening Adjusted for Nonattendance and Contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *European urology* 2009; 56(4):584-591.

(31) van Leeuwen PJ, Connolly D, Gavin A, Roobol M, Black A, Bangma C et al. Prostate cancer mortality in screen and clinically detected prostate cancer: Estimating the screen benefits. *Eur J Cancer* 2010; 46:377-383.

(32) Roemeling S, Kranse R, Vis AN, Gosselaar C, van der Kwast TH, Schroder FH et al. Metastatic disease of screen-detected prostate cancer : characteristics at diagnosis. *Cancer* 2006; 107(12):2779-2785.

(33) National Library of Medicine. Medical Subject Headings (MeSH). US National Institute of Health [2008 Available from: URL:http://www.nlm.nih.gov/pubs/factsheets/mesh.html

(34) Perez-Niddam K, Thoral F, Charvet-Protat S. Economic evaluation of a prostate cancer screening program in France: a decision model. *Crit Rev Oncol Hematol* 1999; 32(2):167-173.

(35) Holmberg H, Carlsson P, Lofman O, Varenhorst E. Economic evaluation of screening for prostate cancer: a randomized population based programme during a 10-year period in Sweden. *Health Policy* 1998; 45(2):133-147.

(36) Kobayashi T, Goto R, Ito K, Mitsumori K. Prostate cancer screening strategies with re-screening interval determined by individual baseline prostate-specific antigen values are cost-effective. *European Journal of Surgical Oncology* 2007; 33(6):783-789.

(37) Krahn MD, Mahoney JE, Eckman MH, Trachtenberg J, Pauker SG, Detsky AS. Screening for prostate cancer. A decision analytic view. *JAMA* 1994; 272(10):773-780.

(38) Coley CM, Barry MJ, Fleming C, Fahs MC, Mulley AG. Early detection of prostate cancer. Part II: Estimating the risks, benefits, and costs. American College of Physicians. *Ann Intern Med* 1997; 126(6):468-479.

(39) Ross KS, Carter HB, Pearson JD, Guess HA. Comparative efficiency of prostate-specific antigen screening strategies for prostate cancer detection. *JAMA* 2000; 284(11):1399-1405.

(40) Ross KS, Guess HA, Carter HB. Estimation of treatment benefits when PSA screening for prostate cancer is discontinued at different ages. *Urology* 2005; 66(5):1038-1042.

(41) Tsodikov A, Szabo A, Wegelin J. A population model of prostate cancer incidence. *Stat Med* 2006; 25(16):2846-2866.

(42) University of Michigan. University of Michigan: CISNET Prostate Cancer Model Profile. 28-10-2008. CISNET.

(43) Etzioni R, Cha R, Cowen ME. Serial prostate specific antigen screening for prostate cancer: a computer model evaluates competing strategies. *J Urol* 1999; 162(3 Pt 1):741-748.

(44) Etzioni R, Gulati R, Falcon S, Penson DF. Impact of PSA screening on the incidence of advanced stage prostate cancer in the United States: a surveillance modeling approach. *Med Decis Making* 2008; 28(3):323-331.

(45) Fred Hutchinson Cancer Research Center. Fred Hutchinson Cancer Research Center (PCSIM): CISNET Prostate Cancer Model Profile. 24-10-2008. CISNET.
Ref Type: Report

(46) Fred Hutchinson Cancer Research Center. Fred Hutchinson Cancer Research Center (PSAPC): CISNET Prostate Cancer Model Profile. 6-8-2009. CISNET.

(47) Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009; 101(6):374-383.

(48) Draisma G, Postma R, Schroder FH, van der Kwast TH, de Koning HJ. Gleason score, age and screening: modeling dedifferentiation in prostate cancer. *Int J Cancer* 2006; 119(10):2366-2371.

(49) Draisma G, de Koning HJ. MISCAN: estimating lead-time and over-detection by simulation. *BJU Int* 2003; 92 Suppl 2:106-111.

(50) Draisma G, Boer R, Otto SJ, van dC, I, Damhuis RA, Schroder FH et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003; 95(12):868-878.

(51) Sandblom G, Varenhorst E, Löfman O, Rosell J, Carlsson P. Clinical consequences of screening for prostate cancer: 15 Years follow-up of a randomised controlled trial in Sweden. *European urology* 2004; 46(6):717-723.

(52) Holmberg H, Carlsson P, Kalman D, Varenhorst E. Impact on health service costs of medical technologies used in management of prostatic cancer. *Scand J Urol Nephrol* 1998; 32(3):195-199.

(53) Kattan MW, Cowen ME, Miles BJ. A decision analysis for treatment of clinically localized prostate cancer. *J Gen Intern Med* 1997; 12(5):299-305.

(54) Fleming C, Wasson JH, Albertsen PC, Barry MJ, Wennberg JE. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. *JAMA* 1993; 269(20):2650-2658.

(55) Cowen ME, Chartrand M, Weitzel WF. A Markov model of the natural history of prostate cancer. *Journal of clinical epidemiology* 1994; 47(1):3-21.

(56) Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993; 270(7):860-864.

(57) US National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Program. SEER [2009 Available from: URL:http://seer.cancer.gov/

(58) Inoue LYT, Etzioni R, Slate EH, Morrell C, Penson DF. Combining longitudinal studies of PSA. *Biostatistics* 2004; 5(3):483-500.

(59) National Center for Health Statistics. Vital statistics of the United States, 1992, Vol. II Sec 6, life tables. Washington (DC): Public Health Service; 1996.

(60) Vogelaar I, van BM, Schrag D, Boer R, Winawer SJ, Habbema JD et al. How much can current interventions reduce colorectal cancer mortality in the U.S.? Mortality projections for scenarios of risk-factor modification, screening, and treatment. *Cancer* 2006; 107(7):1624-1633.

(61) Rijnsburger AJ, van Oortmarssen GJ, Boer R, Draisma G, To T, Miller AB et al. Mammography benefit in the Canadian National Breast Screening Study-2: a model evaluation. *Int J Cancer* 2004; 110(5):756-762.

(62) van den Akker-van Marle ME, van BM, van Oortmarssen GJ, Boer R, Habbema JD, van den Akker-van Marle et al. Cost-effectiveness of cervical cancer screening: comparison of screening policies. *J Natl Cancer Inst* 2002; 94(3):193-204.

(63) Simul8 [computer program] (Version 15) [Boston, MA: 2008.

(64) Bayesian calibration of a natural history model for colorectal cancer. 2009.

(65) Microsoft Coporation. Microsoft Office Excel 2007 [computer program]. [Version 12.0]. 2006.

(66) Office for National Statistics. Cancer statistics registrations: Series MB1 no. 35. 2006.
Ref Type: Online Source

(67) Moore AL, Dimitropoulou P, Lane A, Powell PH, Greenberg DC, Brown CH et al. Population-based prostate-specific antigen testing in the UK leads to a stage migration of prostate cancer. *BJU Int* 2009; 104(11):1592-1598.

(68) Office for National Statistics. Interim Life Tables, England & Wales, 1980-82 to 2006-08. 2010.

(69) NICE. Guide to the methods of technology appraisal. 2008.
Ref Type: Report

(70) Personal Social Services Research Unit (PSSRU). Unit costs of health and social care 2009. http://www pssru ac uk/pdf/uc/uc2009/uc2009_inflationindices pdf [2009

(71) Department of Health. NHS reference costs 2008-09. http://www dh gov uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591 [2010

(72) Department of Health. HRG National tariff 2008/09. http://www dh gov uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081096 [2007

(73) National Institute for Health and Clinical Excellence (NICE). Improving Outcomes in Urological Cancers - Manual. 19-9-2002.

(74) Kestin LL, Vicini FA, Martinez AA. Practical application of biochemical failure definitions: what to do and when to do it. *Int J Radiat Oncol Biol Phys* 2002; 53(2):304-315.

(75) British Association of Urological Surgeons (BAUS). http://www baus org uk/ [2010

(76) Health and Social Care Information Centre. Prescription Cost Analysis 2008. http://www ic nhs uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-2008 [9 A.D.

(77) British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. 57. 2009.

(78) Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer. *Health Technology Assessment* 2007; 11(2):1-198.

(79) Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schroder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology* 2002; 60(5):826-830.

(80) Alibhai SM, Leach M, Tomlinson G, Krahn MD, Fleshner N, Naglie G. Rethinking 30-day mortality risk after radical prostatectomy. *Urology* 2006; 68(5):1057-1060.

(81) Wilt TJ, Shamliyan T, Taylor B, MacDonald R, Tacklind J, Rutks I et al. Comparative effectiveness of therapies for clinically localized prostate cancer. 08-EHC010-EF. 2008. Agency for Healthcare Research and Quality.
Ref Type: Report

(82) Hoffman RM, Hunt WC, Gilliland FD, Stephenson RA, Potosky AL. Patient satisfaction with treatment decisions for clinically localized prostate carcinoma. Results from the Prostate Cancer Outcomes Study. *Cancer* 2003; 97(7):1653-1662.

(83) Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst* 2004; 96(18):1358-1367.

(84) Smith DP, King MT, Egger S, Berry MP, Stricker PD, Cozzi P et al. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. *BMJ* 2009; 339:b4817.

(85) Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlen BJ et al. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002; 347(11):790-796.

(86) Collin SM, Metcalfe C, Donovan J, Lane JA, Davis M, Neal D et al. Associations of lower urinary tract symptoms with prostate-specific antigen levels, and screen-detected localized and advanced prostate cancer: a case-control study nested within the UK population-based ProtecT (Prostate testing for cancer and Treatment) study. *BJU International* 2008; 102(10):1400-1406.

(87) McGrother CW, Donaldson MM, Shaw C, Matthews RJ, Hayward TA, Dallosso HM et al. Storage symptoms of the bladder: prevalence, incidence and need for services in the UK. *BJU Int* 2004; 93(6):763-769.

(88) Korfage IJ, Roobol M, de Koning HJ, Kirkels WJ, Schroder FH, Essink-Bot ML. Does "normal" aging imply urinary, bowel, and erectile dysfunction? A general population survey. *Urology* 2008; 72(1):3-9.

(89) Prins J, Blanker MH, Bohnen AM, Thomas S, Bosch JL. Prevalence of erectile dysfunction: a systematic review of population-based studies. *Int J Impot Res* 2002; 14(6):422-432.

(90) Green JS, Holden ST, Ingram P, Bose P, St George DP, Bowsher WG. An investigation of erectile dysfunction in Gwent, Wales. *BJU Int* 2001; 88(6):551-553.

(91) Seidenfeld J, Samson DJ, Hasselblad V, Aronson N, Albertsen PC, Bennett CL et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000; 132(7):566-577.

(92) Taylor LG, Canfield SE, Du XL. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. *Cancer* 2009; 115(11):2388-2399.

(93) Hummel S, Simpson EL, Hemingway P, Stevenson M, Rees A. Intensity modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. HTA. In press 2010.

(94) Shimizu F, Fujino K, Ito YM, Fukuda T, Kawachi Y, Minowada S et al. Factors associated with variation in utility scores among patients with prostate cancer. *Value in Health* 2008; 11(7):1190-1193.

(95) Krahn M, Ritvo P, Irvine J, Tomlinson G, Bremner KE, Bezjak A et al. Patient and community prefereneces for outcomes in prostate cancer: implications for clinical policy. *Med Care* 2003; 41(1):153-164.

(96) Sullivan PW, Mulani PM, Fishman M, Sleep D, Sullivan PW, Mulani PM et al. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. *Qual Life Res* 2007; 16(4):571-575.

(97) Ara R, Brazier J. Health related quality of life by age, gender and history of cardiovascular disease: resuts from the health survey of England. 09/12. 2009.

(98) Wilt TJ, Brawer MK, Barry MJ, Jones KM, Kwon Y, Gingrich JR et al. The Prostate cancer Intervention Versus Observation Trial:VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. *Contemp Clin Trials* 2009; 30(1):81-87.

(99) Bill-Axelson A, Holmberg L, Filen F, Ruutu M, Garmo H, Busch C et al. Radical Prostatectomy Versus Watchful Waiting in Localized Prostate Cancer: the Scandinavian Prostate Cancer Group-4 Randomized Trial. *jnci* 2008; 100(16):1144-1154.

(100) Cookson MS, Aus G, Burnett AL, Canby-Hagino E, D'Amico AV, Dmochowski RR et al. Variation in the definition of biochemical recurrence in patients treated for localized prosate cancer: the American Urological Association Prostate Guidelines for nLocalized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol* 2007; 177:540-545.

(101) Amling CL. Advanced prostate cancer treatment guidelines: A United States perspective. *BJU International, Supplement* 2004; 94(3):7-8.

(102) American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: Guidelines for PSA following radiation therapy. *International Journal of Radiation Oncology*Biology*Physics* 1997; 37(5):1035-1041.

(103) Rosario DJ, Lane JA, Metcalfe C, Catto JW, Dedman D, Donovan JL et al. Contribution of a single repeat PSA test to prostate cancer risk assessment: experience from the ProtecT study. *European urology* 2008; 53(4):777-784.

(104) Heijnsdijk EA, der KA, Wever EM, Draisma G, Roobol MJ, de Koning HJ et al. Overdetection, overtreatment and costs in prostate-specific antigen screening for prostate cancer. *Br J Cancer* 2009; 101(11):1833-1838.

(105) Alibhai SM, Leach M, Tomlinson G, Krahn MD, Fleshner N, Naglie G. Rethinking 30-day mortality risk after radical prostatectomy. *Urology* 2006; 68(5):1057-1060.

(106) BAUS Cancer Registry. Analyses of minimum data set for urological cancers: Jan 1st - Dec 31st 2008. 2009.

(107) SPSS Inc. SPSS [computer program]. [Version 14.0.1]. 15-11-2005. Chicago, US.

Appendix A: PCa Staging Systems

TNM Staging System

Primary tumour, clinical (T)

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically unapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histological finding in less than or equal to 5% of tissue resected
T1b	Tumour incidental histological finding in greater than 5% of tissue resected
T1c	Tumour identified by needle biopsy (because of elevated PSA level); tumours found in one or both lobes by needle biopsy but not palpable or reliably visible by imaging
T2	Tumour confined within prostate
T2a	Tumour involving less than or equal to half a lobe
T2b	Tumour involving more than half a lobe but not more than one lobe
T2c	Tumour involving both lobes
T3	Tumour extending through the prostatic capsule; no invasion into the prostatic apex or into, but not beyond, the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invading seminal vesicle(s)
T4	Tumour fixed to or invading adjacent structures other than seminal vesicles (e.g. bladder neck, external sphincter, rectum, levator muscles, pelvic wall)

Primary tumour, pathological (pT)

pT2	Organ-confined
pT2a	Tumour involves half of one lobe, but not both lobes
pT2b	Tumour involves more than half of one lobe, but not both lobes
pT2c	Tumour involves both lobes
pT3	Extraprostatic extension
pT3a	Extraprostatic extension
pT3b	Seminal vesicle invasion
pT4	Invasion of bladder, rectum

Regional lymph nodes (N)

NX	Regional lymph nodes (cannot be assessed)
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node or nodes

Distant metastasis (M)

PM1c	More than one site of metastasis present
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Jewett-Whitmore Staging System

Stage A	Very early and without symptoms; cancer cells confined to the prostate
A1	Well-differentiated and slightly abnormal cancer cells
A2	Moderately or poorly differentiated and abnormal cancer cells in several locations within the prostate
Stage B	Confined to the prostate, but palpable (detectable by digital rectal examination) and/or detectable by elevated PSA
B0	Confined to the prostate, non-palpable; PSA elevated
B1	Single cancerous nodule in one lobe of the prostate
B2	Extensive, involvement in one or both prostate lobes
Stage C	Cancer cells found outside the prostate capsule (membrane covering the prostate); spread confined to surrounding tissues and/or seminal vesicles
C1	Extends outside the prostate capsule
C2	Bladder or urethral obstruction
Stage D	Metastasis (spread) to regional lymph nodes or to distant bones, organs (e.g. liver, lungs) and/or other tissues
D0	Metastatic, clinically localised and showing elevated blood PAP levels
D1	Regional lymph nodes involved
D2	Distant lymph nodes, bones or organs involved
D3	Metastatic disease after treatment

Appendix B: Model Search Strategy

The Medline search strategy used in the final literature search (from 1950 to August Week 1 2009):

No.	Search term(s)	Results
1	Models, Theoretical/	75068
2	Models, Biological/	212115
3	Models, Genetic/	45981
4	Models, Animal/	19299
5	Models, Statistical/	43936
6	likelihood functions/	11661
7	linear models/	31940
8	logistic models	52026
9	nomograms/	485
10	proportional hazards models/	24194
11	models, economic/	3628
12	monte carlo method/	12751
13	area under curve/	16588
14	exp Probability/	659233
15	exp risk/	582757
16	uncertainty/	2918
17	exp Regression Analysis/	190342
18	exp "Sensitivity and Specificity"/	295128
19	Stochastic Processes/	7165
20	markov chains/	5769
21	exp survival analysis/	101020
22	Disease-Free Survival/	25493
23	Computational Biology/	20827
24	algorithms/	104688
25	exp "Costs and Cost Analysis"/	145398
26	exp Decision Support Techniques/	42257
27	Computer Simulation/	88141
28	mathematical computing/	5317
29	Numerical Analysis, Computer-Assisted/	3142
30	Decision Trees/	6985
31	natural history model*.tw.	47
32	survival model*.tw.	944
33	screening model*.tw.	507
34	disease progression model*.tw.	28
35	mortality model*.tw.	221

36	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	1677138
37	exp Neoplasms/	2067429
38	36 and 37	245232
39	limit 38 to yr="1994 -Current"	204952
40	exp Prostatic Neoplasms/	67309
41	(prostat$ adj5 (cancer$ or carcin$ or tumor$ or tumour$ or neoplasm$)).tw.	63370
42	((carcinoma or neoplasia or neoplasm$ or adencarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 prostat$).tw.	61284
43	40 or 41 or 42	78175
44	43 and 39	14457
45	Prostate-Specific Antigen/	13867
46	Neoplasm Staging/	85968
47	gleason score*.tw.	3736
48	47 or 46 or 45	98969
49	44 and 48	6483
50	limit 49 to english language	5944
51	limit 50 to humans	5933
52	exp Mass Screening/	96139
53	screening.ab,ti.	217771
54	52 or 53	260985
55	54 and 51	1061

Appendix C: Correlation between model input parameters

	PCancerIncidence	*Well_dwell beta*	*ln(Well_dwell alpha)*	*Prob G1*	*Prob G2 | notG1*	*Local_dwell beta*	*ln(Local_dwell alpha)*	*HzG2*	*HzG3*	*LocalAdv_dwell beta*	*ln(LocalAdv_dwell alpha)*	*Mets_dwell beta*	*HzLocal->Clinical*	*HzLA->Clinical*	*HzMets->Clinical*	*PSASensLocal*	*PSASensLAM*	*HzTxClinLocal/LA*	*HzTxMets*	*HzTxSDLocal/LA*	*RottShift*
PCancerIncidence	1.000																				
Well_dwell beta	0.099	1.000																			
ln(Well_dwell alpha)	-0.783	-0.109	1.000																		
Prob G1	-0.419	0.067	0.381	1.000																	
Prob G2 | notG1	-0.575	0.573	0.431	0.441	1.000																
Local_dwell beta	0.115	-0.342	-0.045	0.372	-0.161	1.000															
ln(Local_dwell alpha)	0.794	-0.236	-0.747	-0.695	-0.703	0.065	1.000														
HzG2	0.615	0.583	-0.681	-0.314	0.033	-0.059	0.456	1.000													
HzG3	-0.529	0.039	0.397	0.264	0.666	0.308	-0.383	-0.144	1.000												
LocalAdv_dwell beta	0.637	-0.328	-0.714	-0.459	-0.739	-0.095	0.787	0.224	-0.586	1.000											
ln(LocalAdv_dwell alpha)	-0.594	-0.147	0.455	0.141	0.485	-0.256	-0.430	-0.434	0.527	-0.336	1.000										
Mets_dwell beta	0.547	0.118	-0.495	0.025	-0.094	0.558	0.438	0.555	0.190	0.159	-0.354	1.000									
HzLocal->Clinical	-0.769	0.343	0.721	0.642	0.793	-0.062	-0.970	-0.344	0.463	-0.845	0.436	-0.379	1.000								
HzLA->Clinical	0.438	-0.416	-0.343	-0.501	-0.726	-0.274	0.613	-0.080	-0.617	0.705	-0.089	-0.097	-0.686	1.000							
HzMets->Clinical	0.568	-0.327	-0.406	-0.180	-0.541	0.479	0.567	0.270	-0.159	0.367	-0.395	0.519	-0.560	0.163	1.000						
PSASensLocal	-0.728	0.484	0.661	0.449	0.756	-0.298	-0.897	-0.221	0.323	-0.771	0.392	-0.462	0.926	-0.578	-0.657	1.000					
PSASensLAM	-0.206	-0.218	0.329	-0.068	-0.309	-0.309	-0.167	-0.455	-0.402	-0.026	-0.033	-0.460	0.043	0.421	-0.252	0.161	1.000				
HzTxClinLocal/LA	0.806	0.013	-0.738	-0.669	-0.538	-0.070	0.906	0.603	-0.380	0.673	-0.409	0.523	-0.863	0.557	0.462	-0.741	-0.140	1.000			
HzTxMets	0.095	0.232	-0.270	-0.543	0.216	-0.201	0.409	0.442	0.372	0.086	0.175	0.274	-0.271	0.056	-0.072	-0.161	-0.417	0.454	1.000		
HzTxSDLocal/LA	0.486	0.430	-0.543	-0.210	-0.149	-0.428	0.352	0.568	-0.522	0.406	-0.347	0.134	-0.343	0.290	0.085	-0.158	-0.019	0.473	0.137	1.000	
RottShift	0.567	0.171	-0.725	-0.522	-0.192	-0.060	0.770	0.655	-0.057	0.562	-0.342	0.480	-0.688	0.209	0.302	-0.598	-0.471	0.753	0.679	0.442	1.000

Appendix D: Impact model parameters

Cost parameters

Item	Source	Data submissions	Average cost	Lower quartile	Upper quartile	Cost year	MFF inflator (mean) National	Inflation factor	Distribution	se	alpha	beta	Inflated mean cost
PSA test	Northern General Hostpital, Sheffield		£11.06			2010	1.00	1.00	gamma	2.21	25.00	0.44	**£11.06**
GP attendance	Curtis 2009		£36.00			2007/8	1.00	1.07	gamma	18.00	4.00	9.00	**£38.64**
Urology outpatient	National reference costs 2010	165	£127.00	£98.00	£153.00	2008/09	1.00	1.07	normal	3.17			**£136.30**
Nurse (GP practice)	Curtis 2009		£11.00			2007/8	1.00	1.07	gamma	5.50	4.00	2.75	**£11.81**
CT scan (one area)	National reference costs 2010	145	£111.49	£86.07	£123.30	2008/09	1.00	1.03	normal	2.29			**£114.64**
Bone scan	National reference costs 2010	118	£168.22	£115.79	£214.11	2008/09	1.00	1.03	normal	6.71			**£172.97**
Dexa scan	National reference costs 2010	99	£75.02	£49.75	£84.20	2008/09	1.00	1.03	normal	2.57			**£77.14**
MRI scan	National reference costs 2010	133	£204.81	£137.55	£257.19	2008/09	1.00	1.03	normal	7.69			**£210.59**
Prostate biopsy	HRG National tarrif 2008-09		£266.00			2008/09	1.12	1.03	fixed				**£307.43**
Radical prostatectomy	HRG National tarrif 2008-09		£3,934.00			2008/09	1.12	1.03	fixed				**£4,546.67**
Radiotherapy	National reference costs 2010	29	£128.71	£83.56	£168.04	2008/09	1.00	1.03	normal	11.63			**£132.34**
Radiotherapy planning	National reference costs 2010	27	£471.22	£227.00	£637.98	2008/09	1.00	1.03	normal	58.63			**£484.53**
Goserelin Acetate 10.8 mg (3 month)	BNF 57 2009		£267.48			2009	1.00	1.00	fixed				**£267.48**
Hospital admission for infection following biopsy	National reference costs 2010	430	£2,374.78	£1,522.62	£2,811.82	2008/09	1.00	1.03	normal	46.09			**£2,441.83**
Hormone refractory/metastatic annual	Collins 2007 (based on TAX327 trial)		£6,476.32			2003/4	1.00	1.22	gamma	3238.16	4.00	1619.08	**£7,909.25**
Prostate cancer death	Collins 2007 (based on TAX327 trial)		£3,528.00			2003/5	1.00	1.22	gamma		4.00	882.00	**£4,308.60**

Screening parameters

Ratio cancers detected to men screened, % men screen positive, % screen positive refuse biopsy: all from ProtecT trial data. Count data used for Beta distributions.

The rate of admission to hospital for infection following biopsy was taken from Raajimakers 2002[23], mean 0.00465, Beta distribution alpha=27, beta=5775.

Treatment

Treatment - Localised cancers

Deterministic proportions derived from BAUS data 2008 (see Appendix E) (assuming no patients G<8 have HT)

Age	Gleason	RP	RT	HT	RT + HT	AM / WW	Other / Unknown
Age <=69	<7	22.22%	13.71%	0.00%	0.00%	30.67%	33.40%
Age 70-79	<7	3.18%	13.28%	0.00%	0.00%	47.75%	35.78%
Age 80+	<7	0.00%	0.90%	0.00%	0.00%	56.11%	42.99%
Age <=69	7	29.41%	22.03%	0.00%	0.00%	18.24%	30.33%
Age 70-79	7	4.01%	25.74%	0.00%	0.00%	36.25%	34.00%
Age 80+	7	0.37%	1.12%	0.00%	0.00%	50.75%	47.76%
Age <=69	>7	16.67%	2.71%	34.11%	20.16%	2.71%	23.64%
Age 70-79	>7	1.97%	1.69%	53.24%	22.25%	3.66%	17.18%
Age 80+	>7	0.56%	0.00%	60.11%	0.56%	7.30%	31.46%

Effective proportions used for calculation of costs and adverse events –allocation of other/unknown pro rata to other treatments

Age	Gleason	RP	RT	HT	RT + HT	AM / WW	Other / Unknown
Age <=69	<7	33.37%	20.59%	0.00%	0.00%	46.04%	0.00%
Age 70-79	<7	4.96%	20.68%	0.00%	0.00%	74.36%	0.00%
Age 80+	<7	0.00%	1.59%	0.00%	0.00%	98.41%	0.00%
Age <=69	7	42.21%	31.62%	0.00%	0.00%	26.18%	0.00%
Age 70-79	7	6.08%	39.00%	0.00%	0.00%	54.92%	0.00%
Age 80+	7	0.71%	2.14%	0.00%	0.00%	97.14%	0.00%
Age <=69	>7	21.83%	3.55%	44.67%	26.40%	3.55%	0.00%
Age 70-79	>7	2.38%	2.04%	64.29%	26.87%	4.42%	0.00%
Age 80+	>7	0.82%	0.00%	87.70%	0.82%	10.66%	0.00%

Note it was assumed that 15% of patients choosing AM go on to have radical treatment (Beta distribution, alpha=11, beta=64)[26]

Stochastic distributions

For the stochastic analysis “Other /Unknown” was set to zero. Matrices for different scenarios were calculated for different assumptions regarding the allocation of Other/unknown pro rata to other treatments, or assuming all had AM/WW, and also whether some men with G<8 are in fact given hormone therapy. This gave four potential matrices. Values were sampled from flat distributions between the minimum and maximum values from the four matrices based on different assumptions (normalised to ensure row totals equal 1). The matrices of minimum and maximum values are shown below.

Minimum values

Age	Gleason	RP	RT	HT	RT + HT	AM / WW
Age <=69	<7	22.22%	8.89%	0.00%	0.00%	42.14%
Age 70-79	<7	3.18%	4.39%	0.00%	0.00%	60.51%
Age 80+	<7	0.00%	0.00%	0.00%	0.00%	73.81%
Age <=69	7	29.41%	5.53%	0.00%	0.00%	9.12%
Age 70-79	7	4.01%	4.96%	0.00%	0.00%	21.29%
Age 80+	7	0.37%	0.00%	0.00%	0.00%	36.43%
Age <=69	>7	16.67%	2.71%	34.11%	20.16%	3.55%
Age 70-79	>7	1.97%	1.69%	53.24%	22.25%	4.42%
Age 80+	>7	0.56%	0.00%	60.11%	0.56%	10.66%

Maximum values

Age	Gleason	RP	RT	HT	RT + HT	AM / WW
Age <=69	<7	33.37%	20.59%	3.91%	7.24%	64.06%
Age 70-79	<7	4.96%	20.68%	13.85%	13.85%	83.53%
Age 80+	<7	0.00%	1.59%	24.60%	1.59%	99.10%
Age <=69	7	42.21%	31.62%	17.06%	23.68%	48.57%
Age 70-79	7	6.08%	39.00%	33.63%	31.48%	70.25%
Age 80+	7	0.71%	2.14%	60.71%	2.14%	98.51%
Age <=69	>7	21.83%	3.55%	44.67%	26.40%	26.36%
Age 70-79	>7	2.38%	2.04%	64.29%	26.87%	20.85%
Age 80+	>7	0.82%	0.00%	87.70%	0.82%	38.76%

Treatment - Locally advanced

Proportions of men with known treatment from BAUS 2008. Beta distributions from count data. Note proportion HT = 1 minus proportion RT+HT.

RT + HT	**alpha**	**beta**	**mean**
Age <=69	149	423	0.260
Age 70-79	157	613	0.204
Age 80+	10	531	0.018
HT			
Age <=69			
Age 70-79			
Age 80+			

Adverse effects of treatment

The rates below are taken from Smith 2009.[84] The parameters of the Beta distribution were estimated by applying the proportions affected to the sample sizes.

Sexual dysfunction	**Distribution**	**alpha**	**beta**	**mean**
RP	Beta	673.46	307.54	0.687
RT	Beta	63.63	59.37	0.517
HT	Beta	57.53	3.47	0.943
RT+HT	Max of RT and HT			
AM/WW	Beta	69.21	130.79	0.346
Urinary incontinence				
RP	Beta	109.87	871.13	0.112
RT	Beta	3.32	119.68	0.027
HT	fixed			0
RT+HT	Max of RT and HT			
AM/WW	fixed			0

For bowel function the rate was fixed at zero for all treatments other than radiotherapy. For the latter, a normal distribution was used, mean 0.1, se 0.3.

Excess 30 day mortality following RP

Data from Alibhai *et al.*[105]. The parameters of the Beta distribution were estimated by applying the proportions affected to the sample sizes.

Age	Distribution	alpha	beta	mean
50-59	Beta	5.2	2908.8	0.0018
60-69	Beta	33.6	6553.4	0.0051
70-79	Beta	7.2	1209.8	0.0059

Utility values

Co-efficients for the calculation of baseline age-specific utility was taken from Ara[97].

Item	Co-eff
constant	0.9569784
male	0.0246479
age	-0.0008459
age^2	-0.0000224

Utility values for prostate cancer states

Values taken from Krahn *et al.*[95] for adverse effects, Sullivan *et al.*[96] for hormone-refractory metastatic cancer. Standard error assumed to be 0.5 * mean.

Adverse Effect	Mean	Distribution	mean	se	alpha	beta
Sexual dysfunction	0.9	1-Beta	0.1	0.05	2.60	23.40
Urinary incontinence	0.94	1-Beta	0.06	0.03	2.76	43.24
Bowel complications	0.89	Beta	0.89	0.04	53.46	6.61
Hormone refractory metastatic disease	0.635	1-Beta	0.365	0.1825	1.54	2.68

Other disease/population parameters

Time from PSA progression to locally advanced disease: mean 2.6 years, estimated from Kestin *et al.*[74]. Distribution lognormal, assume ln(se) = 0,5*ln(mean).

Time in hormone refractory disease: mean 1.865 years, 95% CI 1.70 – 2.05, normal. [78]

Population baseline sexual dysfunction: linear function estimated from Korfage *et al*.[88] As there is greater uncertainty than within the data itself (measure of SD, applicability to UK population) with regard to both the constant and the gradient they were allowed to vary independently, with normal distributions of se = 0.05*mean.

Item	Mean	Distribution	se
constant	-0.5320	normal	0.0266
age multiplier	0.0109	normal	0.0005

Resource Use

Resource use has been estimated using the 2008 NICE prostate cancer guideline[7], and clinical advice.

Activity	Item	Mean	Distribution	alpha	beta
PSA screening test	General Practice Nurse	1	Fixed		
	PSA test	1	Fixed		
Discussion of positive PSA test result	GP appointment	1	Fixed		
Monitoring of men who have a positive PSA test but decline biopsy (annual)	PSA test	2	Gamma	1	2
	GP appointment	2	Gamma		
Biopsy	Biopsy	1	Fixed		
	Hosp admission	see above			
Additional diagnostic tests	Bone scan	1	Gamma	1	1
	MRI scan	1	Gamma		
Monitoring of patients with raised PSA but negative biopsy (total)	Biopsy	1	Gamma	1	1
	Hosp admission	see above			
	O/P appointment	3	gamma	1	3
Information Appointment	O/P appointment	1	Fixed		
Radical treatment: RP	O/P appointment	3	gamma	4	0.75
	RP	1	Fixed		
Radical treatment: RT	O/P appointment	3			
	RT planning	1	Fixed		
	RT fractions	37	Fixed		
Radical treatment: RT with neo-adjuvant hormone therapy	O/P appointment	3			
	RT planning	1	Fixed		
	RT fractions	37	Fixed		
	Goserelin	2	Fixed		
Follow up of patients following radical treatment annual	O/P appointment	2	gamma	4	0.5
Watchful waiting annual	PSA test	2	gamma	4	0.5
	GP appointment	2			
Active monitoring annual	Biopsy	0.5	gamma	1	0.5
	Hosp admission	see above			
	O/P appointment	4	gamma	4	1
Additional monitoring of patients post-PSA failure annual	Bone scan	0.5	Fixed		
	CT scan	0.5	Fixed		
	O/P appointment	4	gamma	25	0.16
Annual treatment costs for patients on hormone therapy ((local), locally advanced and metastatic tumours)	General Practice Nurse	4	fixed		
	O/P appointment	2	gamma	4	0.5
	Goserelin Acetate 10.8 mg (3 month)	4	fixed		
	Dexa scan	0.5	gamma	4	0.125

Where alpha =1 it has been assumed that variance is equal to the mean. For all other parameters the variance is assumed to be 0.5*mean, with the exception of patient monitoring post PSA failure, which is estimated as variance = 0.2*mean.

Appendix E: BAUS Data (2008)

Summary data from the British Association of Urological Surgeons for the year 2008 was analysed. 391 consultant urologists from 107 hospitals centres across the UK submitted data on newly presented urological tumours for the period Jan 1st to Dec 31st 2008, which represents 46% of the total number of tumours registered in 2006/2007.[106] 14,695 prostate cancers were reported to BAUS in 2008, of which 63.7% (9357) cancers have stage information (see Table 31). Analysis was conducted on 2008 data as this was the most up to date data which had been validated by BAUS.

Table 31. Stage distribution of BAUS 2008 data

Stage	N	%	Cumulative %
Localised	5878	40.0%	40.0%
Locally Advanced	2,763	18.8%	58.8%
Metastatic	716	4.9%	63.7%
Unknown	5338	36.3%	100.0%
Total	**14695**	**100.00%**	

Age was known for 98.6% of the patients with stage information (equivalent to 62.8% of all prostate cancer reported to BAUS). Of these patients, Gleason score was also known for 96.6% of localised stage patients. Treatment data for 9,027 patients was therefore analysed, however treatment was listed as unknown for 4.8% of patients, “Diagnosis” for 19.8% and “Other” for 1.4%. Note radiotherapy includes brachytherapy, and radical prostatectomy includes the RP + HT combination. 26.0% of patients therefore have treatment other than RP, RT, HT, RT+HT or AM/WW, including men who have surgery other than RP. Tables 32-34 show treatment groups by age and stage. In summary, complete age, stage and treatment information is known for 49.3% of all reported PCa’s to BAUS (or 61.4% including “Diagnosis”).

It can be seen that men are shown to have hormone treatment alone or in combination with radiotherapy for less aggressive (G<8) localised cancers; contrary to the 2008 NICE guidance. This may be due to inaccuracies in the data, or reflect variation in clinical practice.

Factors influencing the quality of the data have been suggested as a result of the increase in the variety of people recording the data apart from consultants and the increasing use of inadequate in-house systems to populate the BAUS dataset which incorporate large gaps in completion.[106]

Table 32. Localised cancers by treatment (BAUS 2008)

Age	Gleason score	N	RP	Surgery	RT	HT	RT + HT	AM / WW	Diagnosis	Other	Unknown
< 70	<7	1,575	22.2%	2.8%	8.9%	2.6%	4.8%	28.1%	22.3%	0.9%	7.4%
	7	1,006	28.5%	2.0%	5.4%	11.5%	16.0%	6.2%	21.2%	0.6%	8.6%
	>7	292	14.7%	3.1%	2.4%	30.1%	17.8%	2.4%	21.2%	0.7%	7.5%
	Total	2,873	23.7%	2.5%	7.0%	8.5%	10.1%	17.8%	21.8%	0.8%	7.8%
70-79	<7	881	3.3%	5.0%	4.5%	9.2%	9.2%	40.2%	24.4%	0.9%	3.3%
	7	847	4.0%	3.3%	5.0%	22.2%	20.8%	14.0%	22.3%	1.1%	7.3%
	>7	422	1.7%	3.6%	1.4%	44.8%	18.7%	3.1%	18.5%	0.9%	7.3%
	Total	2,150	3.3%	4.0%	4.1%	21.3%	15.6%	22.6%	22.4%	1.0%	5.7%
>= 80	<7	187	0.0%	15.0%	0.0%	16.6%	1.1%	49.7%	16.0%	1.1%	0.5%
	7	201	0.5%	6.5%	0.0%	42.3%	1.5%	25.4%	22.9%	1.0%	0.0%
	>7	178	0.6%	6.7%	0.0%	60.1%	0.6%	7.3%	23.6%	0.6%	0.6%
	Total	566	0.4%	9.4%	0.0%	39.4%	1.1%	27.7%	20.8%	0.9%	0.4%
Total	<7	2,643	14.3%	4.4%	6.8%	5.8%	6.0%	33.6%	22.6%	0.9%	5.5%
	7	2,054	15.7%	3.0%	4.7%	18.9%	16.6%	11.3%	21.8%	0.8%	7.3%
	>7	892	5.7%	4.0%	1.5%	43.0%	14.8%	3.7%	20.4%	0.8%	6.1%
	Total	5,589	13.5%	3.8%	5.2%	16.6%	11.3%	20.6%	22.0%	0.9%	6.2%

Table 33. Locally advanced cancers by treatment (BAUS 2008)

Age	N	RP	Surgery	RT	HT	RT + HT	AM / WW	Diagnosis	Other	Unknown
< 70	890	6.3%	1.5%	1.5%	47.5%	15.3%	1.8%	18.4%	3.0%	4.7%
70-79	1,110	1.2%	2.5%	0.7%	55.2%	13.4%	3.4%	19.1%	1.5%	2.9%
>= 80	736	0.1%	2.9%	0.1%	72.1%	1.2%	9.0%	12.9%	1.2%	0.4%
Total	2,736	2.6%	2.3%	0.8%	57.3%	10.7%	4.4%	17.2%	1.9%	2.8%

Table 34. Metastatic cancers by treatment (BAUS 2008)

Age	N	RP	Surgery	RT	HT	RT + HT	AM / WW	Diagnosis	Other	Unknown
< 70	238	0.4%	3.4%	0.8%	67.6%	3.8%	0.8%	15.1%	5.5%	2.5%
70-79	280	0.0%	2.9%	0.0%	75.0%	5.0%	1.1%	11.8%	2.5%	1.8%
>= 80	184	0.0%	4.9%	0.0%	78.3%	2.2%	3.3%	8.7%	2.7%	0.0%
Total	702	0.1%	3.6%	0.3%	73.4%	3.8%	1.6%	12.1%	3.6%	1.6%

Appendix F: SWPHO Data (2000-2006)

Prostate cancer patient level cancer registry data for the whole of England was provided by the South West Public Health Observatory (SWPHO). The cancer registry data was cross-referenced with BAUS data in order to provide as much detail as possible about each patient with regards to treatment. The combined set consisting 705,401 records (384,019 patients) follows subjects over the period 1990-2008. Analysis was conducted on data from 2000-2006 (384,914 records / 202,559 patients) as these years were most complete and PSA testing should be well established. Analysis was carried out in SPSS Version 14.0,[107] and Microsoft Excel 2007.[65] Overall, age, stage, Gleason score and treatment information was poor with just 32.6% of patients having complete data.

Details of each patient included unique patient identifier, cancer registry, year of diagnosis, age at diagnosis (in quinary age bands), cancer stage (localised, locally advanced or metastatic), Gleason score, and various fields relating to treatment. Cancer stage was derived from TNM data by the SWPHO Cancer Analysis Team.

The unique patient identifier was used to link records from the same patient together, thereby allowing information from all fields to be examined; however the order of the records is unknown. This means that the order of treatment undergone by the patient is therefore unknown.

The objective of the analysis was to determine treatment on diagnosis, so the records most likely to reflect this were identified. Where age at diagnosis differed between records, only the earliest records (youngest age band) were used. Similarly, where age at diagnosis was recorded in one or more records, but unknown in another, the unknown records were discarded. The same methodology applied to

cancer stage and Gleason score, with only the earliest records being used; namely the lowest stage or smallest Gleason score respectively.

After filtering the records accordingly, data for 202,558 patients were analysed. Stage was known for 34.3% of subject as shown in Table 35.

Table 35. Stage distribution of SWPHO-BAUS cross-referenced 2000-2006 data

Stage	N	%	Cumulative %
Localised	45773	22.6%	22.6%
Locally Advanced	19848	9.8%	32.4%
Metastatic	3880	1.9%	34.3%
Unknown	133057	65.7%	100.0%
Total	**202558**	**100.00%**	

Patient for whom Death and another form of treatment was listed were included in the analysis, however 2.1% of patients whose only treatment was “Death” were excluded. Despite attempts to find treatment data in multiple patient records, in the remaining 66,042 patients, 14.5% was “Unknown”, 12.4% “Other” and 7.9% “Diagnosis”. In total complete information was known for 32.6% of subject or 21.2% subject excluding those with Unknown/Other/Diagnosis as the only treatment.

Classification methods

For each patient record, treatment was derived from individual fields for radiotherapy, chemotherapy, hormone therapy, surgery, other treatment and no treatment; each of which contained either Yes, No, or Unknown/’Blank’. In addition to these, the field radiotherapy type and treatment type provided extra information in the form of a textual description or code.

All of the treatment fields were examined for each subject, including subjects that had multiple records. The interpretation and recoding of all possible value for each of the treatment related fields is given in Table 36.

Table 36. Classification of raw data into meaningful treatment groups.

Variable	Value	Recoded variable
Treatment type	Surgery	Surgery
	SURGERY	
	Surgical Procedure	
Surgery	Y	
Treatment type	BRACHYTHERAPY	Radiotherapy
	EXTERNAL RADIOTHERAPY	
	OTHER RADIOTHERAPY	
	Radiotherapy	
	Radiotherapy Admission	
	RT	
	TELETHERAPY	
Radiotherapy	Y	
Treatment type	A	Hormone Therapy
	C	
	Chemotherapy	
	CHEMOTHERAPY	
	Chemotherapy admission	
	DRUGS	
	Hormone	
	Hormone therapy	
	HORMONE/ENDOCRINE THERAPY	
	Planned hormone therapy	
Chemotherapy	Y	
Hormone Therapy	Y	
Treatment type	Death certificate initiated consequence	Death
	Found at PM	
	Histological diagnosis from post mortem	
	F	
	Hospice stay	
	Immunotherapy	
	IMMUNOTHERAPY	
	O	
	Other	
	OTHER TREATMENT	
	Palliative Care	
	Surgery for nodes and metastases	
	T	
	Y	

Table 36 continued

Variable	Value	Recoded variable
Treatment type	Additional pathology	Diagnosis
	Biopsy only	
	Clinical diagnosis	
	Cytological diagnosis	
	D	
	Diagnosis	
	Diagnosis from biochemical and immunology	
	Diagnosis from imaging	
	Histological diagnosis of nodes and meta	
	Histological diagnosis of primary	
	Surgical diagnosis	

Where more than one treatment was listed for a patient (other than the common combination of radiotherapy and hormone therapy) the likely primary treatment was selected: for example surgery and hormone therapy was classified as surgery. In the very small number of patients for whom both surgery and radiotherapy were listed, surgery was classed as the primary treatment. RT includes brachytherapy and teletherapy.

Table 37. Localised cancers by treatment type (SWPHO 2000-2006)

Age	Gleason score	N	Surgery	RT	HT	RT + HT	Diagnosis	Other	Unknown
< 70	<7	13,995	40.8%	10.4%	4.4%	12.1%	7.5%	11.4%	13.3%
	7	4,124	36.5%	10.4%	8.0%	15.6%	4.7%	6.5%	18.3%
	>7	1,872	29.2%	7.6%	12.6%	16.4%	5.1%	6.9%	22.2%
	Total	19,991	38.8%	10.1%	5.9%	13.2%	6.7%	10.0%	15.2%
70-79	<7	10,317	28.6%	6.0%	15.1%	10.0%	12.1%	17.2%	11.1%
	7	3,871	22.3%	7.4%	18.7%	12.0%	9.6%	13.1%	16.9%
	>7	2,570	26.1%	4.7%	21.6%	12.1%	7.6%	8.9%	19.0%
	Total	16,758	26.8%	6.1%	16.9%	10.8%	10.8%	15.0%	13.6%
>= 80	<7	3,288	38.8%	0.6%	22.4%	1.6%	13.4%	16.7%	6.4%
	7	1,386	28.1%	0.6%	24.0%	0.9%	16.8%	17.1%	12.5%
	>7	1,390	28.5%	0.6%	29.0%	2.3%	13.6%	11.9%	14.1%
	Total	6,064	34.0%	0.6%	24.3%	1.6%	14.2%	15.7%	9.6%
Total	<7	27,600	36.0%	7.6%	10.5%	10.1%	9.9%	14.2%	11.7%
	7	9,381	29.4%	7.7%	14.7%	12.0%	8.5%	10.8%	16.8%
	>7	5,832	27.7%	4.7%	20.5%	11.1%	8.2%	9.0%	18.8%
	Total	42,813	33.4%	7.2%	12.8%	10.6%	9.4%	12.8%	13.8%

Table 38. Locally advanced cancers by treatment type (SWPHO 2000-2006)

Age	N	Surgery	RT	HT	RT + HT	Diagnosis	Other	Unknown
< 70	7,484	36%	6%	17%	15%	3%	7%	16%
70-79	7,624	21%	5%	28%	9%	6%	12%	19%
>= 80	4,325	19%	2%	36%	3%	8%	17%	16%
Total	19,433	26%	5%	26%	10%	5%	11%	17%

Table 39. Metastatic cancers by treatment type (SWPHO 2000-2006)

Age	N	Surgery	RT	HT	RT + HT	Diagnosis	Other	Unknown
< 70	1,085	21%	7%	25%	21%	4%	10%	12%
70-79	1,495	18%	7%	30%	15%	5%	15%	11%
>= 80	1,216	14%	5%	36%	9%	5%	24%	8%
Total	3,796	18%	6%	30%	14%	5%	16%	10%

Appendix G: Search strategy for utility values for prostate cancer

The following databases were searched:

MEDLINE & MEDLINE In-Process

EMBASE

Cochrane Database of Systematic Reviews

Cochrane Controlled Trials Register

DARE

HTA Database

NHS EED

The search strategy was as follows:

1 Prostatic Neoplasms/

2 (prostat* adj5 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)).tw.

3 ((carcinoma* or neoplasia or neoplasm* or adenocarcinoma* or cancer* or tumor* or tumour* or malignan*) adj3 prostat*).tw.

4 1 or 2 or 3

5 (utillity or utilities or eq5d or eq-5d or europol or qwb or hui2 or hui3 or 15d or sf-6d or sf6d or aqol).mp.

6 4 and 5

7 (200905$ or 200906$ or 200907$ or 200908$ or 200909$ or 200910$ or 200911$ or 200912$ or 2010$).ed.

8 6 and 7

Note that 0 references were found in DARE, HTA and EED.

Appendix H: Calibration Results

Table 40. ONS and East Region Cancer Registry calibration

Figure 18. Calibration of model to Rotterdam age specific incidence[50]

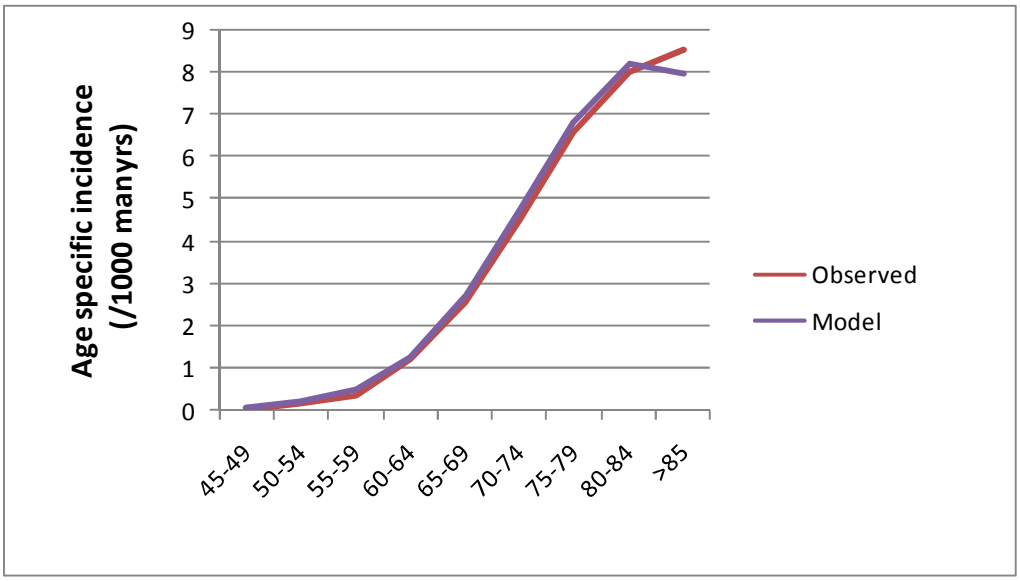


Figure 19. Calibration to Rotterdam stage grade distribution[50]

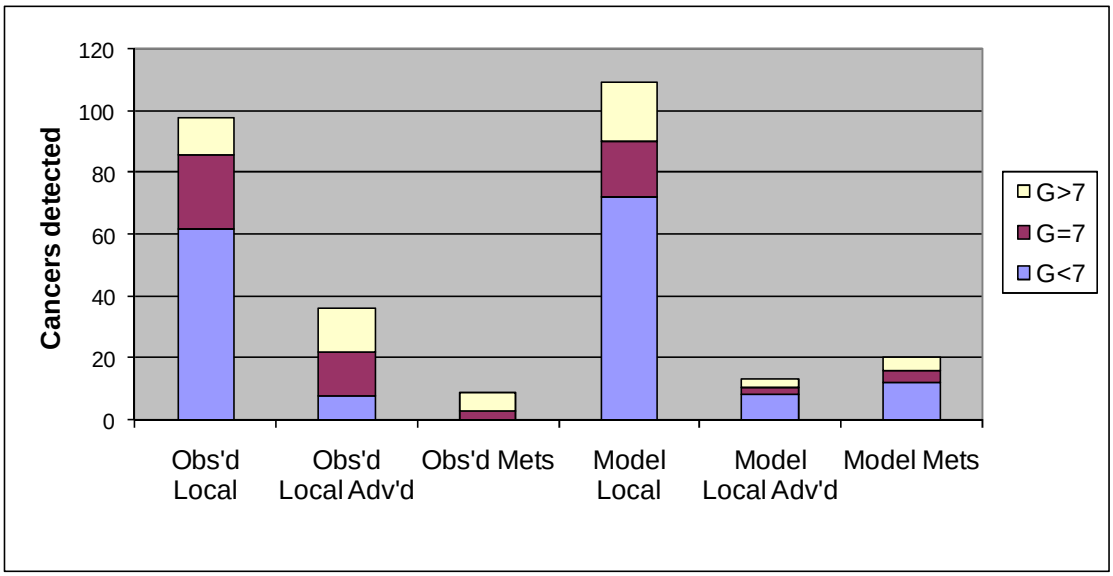


Figure 20. Calibration to progression free and overall survival of screen detected non metastatic cancers.[32]

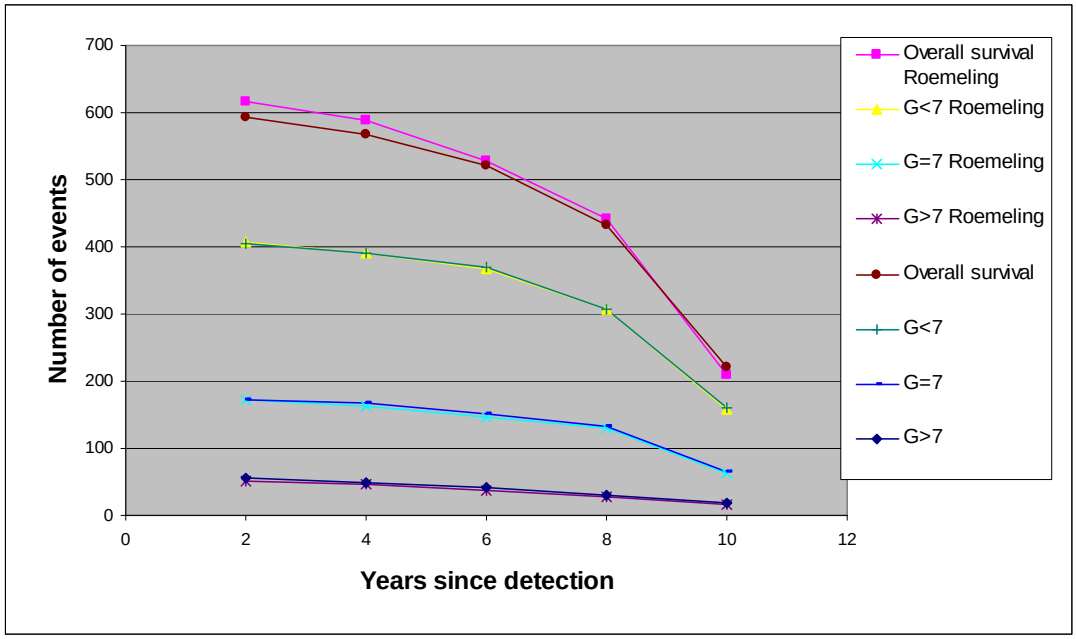
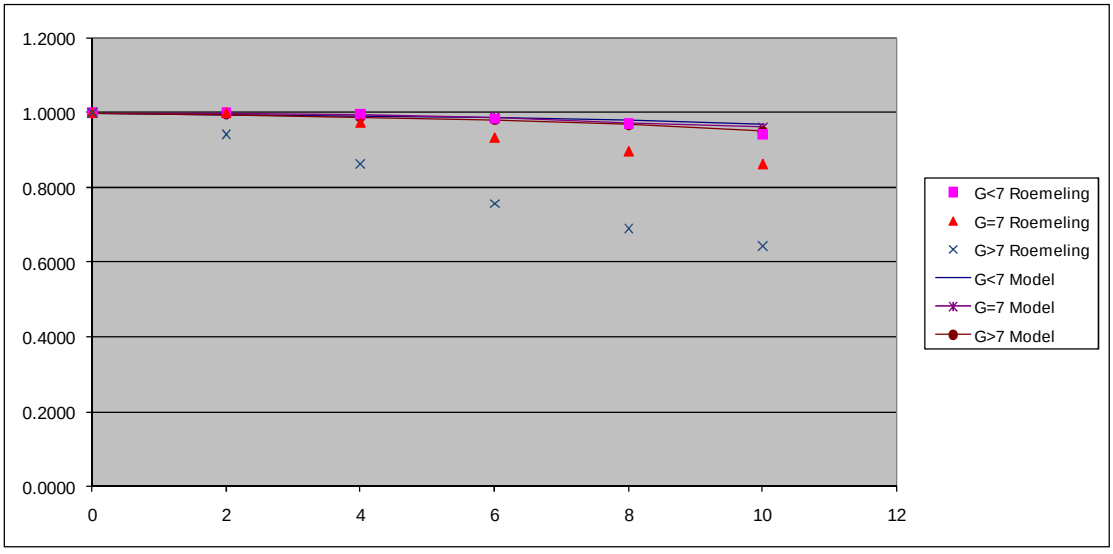


Figure 21. Calibration to metastatic free survival and prostate cancer mortality in the screen detected population.[35]



Appendix I: Clinical cancers, screen detected cancers and incident cancers

Table 41. Detailed results for screening options

Population aged 50 : 401700 Mid year population estimates 2008 ONS

Total cancers : No screening				
G<7	G=7	G>7	Locally advanced	Mets
416.2	140.1	212.3	12.7	17.0
1078.7	314.3	424.7	25.5	59.5
2484.3	662.5	832.4	123.2	216.6
4144.8	1108.4	1159.4	327.0	484.1
5074.8	1320.7	1358.9	696.5	951.3
4365.6	1006.5	1006.5	993.7	1775.1
2412.1	382.2	331.2	1138.1	1902.5
717.7	93.4	51.0	1133.9	1669.0

Screening policy : Once at 50

Screen detected cancers				
Local			Locally advanced	Mets
G<7	G=7	G>7		
419.0	96.0	93.0	44.0	1.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0

Interval cancers				
Local			Locally advanced	Mets
G<7	G=7	G>7		
64.0	21.0	30.0	1.0	2.0
202.0	51.0	81.0	3.0	4.0
525.0	141.0	185.0	12.0	26.0
933.0	255.0	272.0	54.0	86.0
1188.0	311.0	320.0	135.0	190.0
1026.0	237.0	237.0	218.0	393.0
568.0	90.0	78.0	263.0	438.0
169.0	22.0	12.0	267.0	390.0

Table 41 continued. Detailed results for screening options

Screening policy : 50-74 every 4 years

Screen detected cancers				
Local			Locally advanced	Mets
G<7	G=7	G>7		
1092.0	253.0	256.0	74.0	0.0
1182.0	272.0	246.0	60.0	0.0
1709.0	406.0	361.0	69.0	0.0
1837.0	453.0	443.0	118.0	0.0
2422.0	506.0	516.0	274.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0

Interval cancers				
Local			Locally advanced	Mets
G<7	G=7	G>7		
57.0	18.0	37.0	2.0	2.0
92.0	27.0	38.0	0.0	1.0
209.0	61.0	67.0	2.0	8.0
324.0	85.0	111.0	14.0	21.0
354.0	97.0	112.0	30.0	50.0
314.0	66.0	77.0	32.0	87.0
187.0	39.0	24.0	56.0	89.0
56.0	11.0	6.0	65.0	115.0

Screening policy : 50-74 every 2 years

Screen detected cancers				
Local			Locally advanced	Mets
G<7	G=7	G>7		
1276.0	285.0	326.0	71.0	1.0
1337.0	320.0	300.0	27.0	0.0
3081.0	740.0	693.0	46.0	0.0
2137.0	506.0	510.0	42.0	0.0
1597.0	369.0	360.0	52.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0

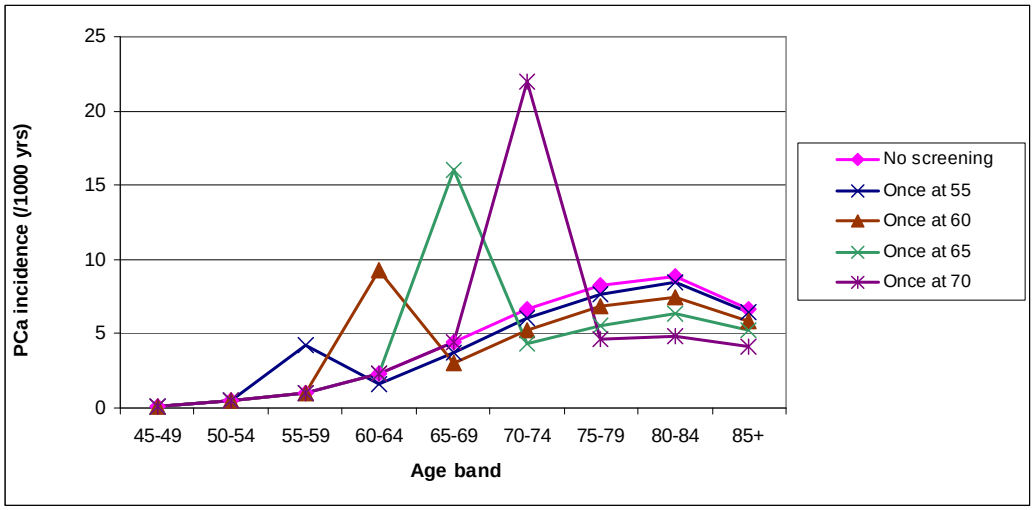
Interval cancers				
Local			Locally advanced	Mets
G<7	G=7	G>7		
42.0	16.0	22.0	3.0	2.0
72.0	19.0	22.0	0.0	1.0
140.0	34.0	39.0	2.0	7.0
231.0	63.0	68.0	13.0	21.0
282.0	64.0	81.0	30.0	49.0
247.0	50.0	66.0	28.0	86.0
132.0	23.0	18.0	52.0	83.0
41.0	8.0	5.0	56.0	95.0

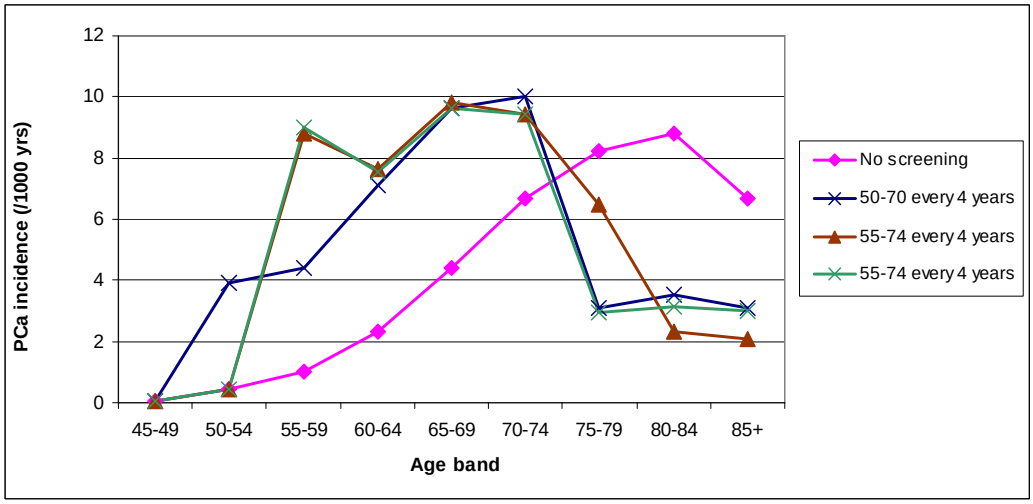
Screening policy : 50-74 every year

Screen detected cancers				
Local			Locally advanced	Mets
G<7	G=7	G>7		
1443.0	338.0	367.0	64.0	2.0
1953.0	462.0	450.0	3.0	0.0
2805.0	661.0	648.0	9.0	0.0
2631.0	652.0	623.0	8.0	0.0
1133.0	236.0	226.0	6.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0

Interval cancers				
Local			Locally advanced	Mets
G<7	G=7	G>7		
32.0	11.0	17.0	2.0	1.0
55.0	15.0	17.0	0.0	1.0
115.0	34.0	33.0	2.0	7.0
204.0	50.0	57.0	13.0	21.0
246.0	58.0	75.0	30.0	49.0
218.0	47.0	60.0	28.0	86.0
116.0	23.0	19.0	51.0	83.0
39.0	8.0	3.0	52.0	96.0

Figure 22. Summary results for alternative screening policies





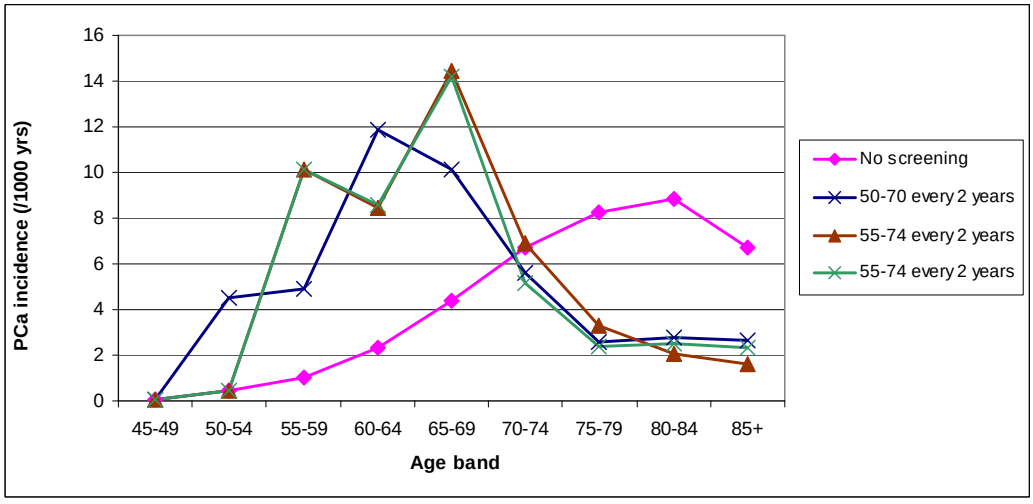


Table 42. Impact of screening on prostate cancer detection

	No screening	Once at 55	Once at 60	Once at 65	Once at 70	50-70 every 4 years	55-74 every 4 years	55-74 every 4 years	50-70 every 2 years	55-74 every 2 years	55-74 every 2 years
Lifetime probability of Pca	10.2%	10.6%	11%	12.3%	12.9%	14.9%	16%	15.1%	15.6%	16%	15.9%
Proportion of people screen detected with PCa who would have died of other causes (Overdetection)		24%	32%	41%	47%	42%	45%	43%	43%	45%	44%
Proportion of people screen detected who would have been diagnosed later with clinical PCa (Potentially relevant)		76%	68%	59%	53%	58%	55%	57%	57%	55%	56%
Mean lead time for PCs diagnosis in overdetected cases (yrs)		15.0	13.4	11.5	9.6	12.1	11.6	12.0	12.8	12.3	12.6
Mean lead time for PCa diagnosis in potentially relevant cases (yrs)		13.1	12.2	9.9	8.1	12.0	11.1	11.5	12.9	12.1	12.3

Figure 23. Age specific prostate cancer mortality

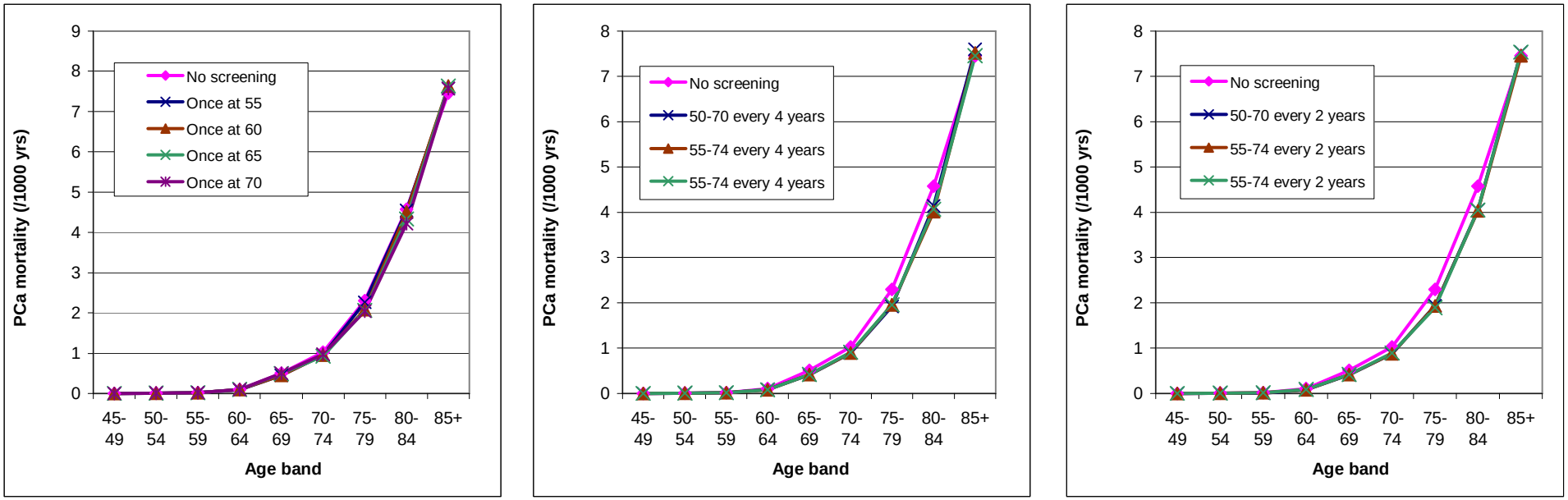


Table 43. Impact of screening on duration of prostate cancer management – potentially relevant cancers

	Once at 55	Once at 60	Once at 65	Once at 70	50-70 every 4 years	55-74 every 4 years	55-74 every 4 years	50-70 every 2 years	55-74 every 2 years	55-74 every 2 years
Average treatment duration for screen detected potentially relevant cancers under a policy of no screening	10.6	8.7	7.6	6.2	8.9	8.5	8.7	9.2	8.7	8.9
Average treatment duration for screen detected potentially relevant cancers under screening	24.2	21.3	17.9	14.6	21.3	20.0	20.5	22.4	21.2	21.5
Average marginal treatment duration under screening	13.5	12.6	10.3	8.4	12.4	11.5	11.8	13.2	12.4	12.6
Average lead time	13.1	12.2	9.9	8.1	12.0	11.1	11.5	12.9	12.1	12.3
Average life years gained consequent on screening for potentially relevant cancers	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Table 44. Impact of screening on duration of prostate cancer management – cohort of men aged 50 years

	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year	Once at 55	Once at 60	Once at 65	Once at 70	50-70 every 4 years	55-74 every 4 years	55-74 every 4 years	50-70 every 2 years	55-74 every 2 years	55-74 every 2 years
Total invited	401700	401700	401700	401700	401700	401700	401700	401700	401700	401700	401700	401700	401700	401700
Total screened at least once	320618	320618	320618	320618	311742	298559	277588	246220	320235	311742	311742	320235	311742	311742
Total overdetected cancers	493	23590	26975	28695	1673	4468	8936	11722	20139	23740	21201	23231	26900	24437
Total years of overmanagement in cohort	7473	274701	336621	373227	25040	59767	103137	112659	243779	275820	253652	298376	329845	306999
Expected years of overmanagement per person screened	0.023	0.857	1.050	1.164	0.080	0.200	0.372	0.458	0.761	0.885	0.814	0.932	1.058	0.985
Total potentially relevant cancers in cohort identified by screening	2280	29701	32802	33817	5241	9522	12885	13386	27749	29593	27681	31181	32455	31121
Total life yrs gained in cohort	1127	9268	9710	9890	2329	4184	4567	4238	9293	9179	8943	9736	9905	9605
Avg life yrs gained per person screened	0.0035	0.0289	0.0303	0.0308	0.0075	0.0140	0.0165	0.0172	0.0290	0.0294	0.0287	0.0304	0.0318	0.0308
Extra years Pca management in cohort	32581	345851	413233	452554	68617	115934	127894	107780	333921	329858	317886	401243	393188	382113
Average extra potentially relevant Pca management years per person screened	0.10	1.08	1.29	1.41	0.22	0.39	0.46	0.44	1.04	1.06	1.02	1.25	1.26	1.23
Average extra years of Pca management per life year gained	35.53	66.95	77.22	83.50	40.21	42.00	50.58	52.01	62.16	65.98	63.91	71.86	73.00	71.75

Appendix J: Additional patient interventions for screening compared to no screening

Baseline policies 1-4

	Radical prostatectomy	Radical radiotherapy	Radical radiotherapy & HT	Hormone Therapy	Active monitoring	Watchful waiting	Other local treatment
Policy 1 :Once at age 50	377	218	1	578	317	-19	465
Policy 2 : Every 4 years from 50 - 74	7180	4888	1142	14938	5966	1079	9798
Policy 3 : Every 2 years from 50 - 74	9727	5796	935	16805	8227	-1162	11391
Policy 4 : Every year from 50 - 74	11171	6186	893	17193	9560	-2837	12001

Screening once

	Radical prostatectomy	Radical radiotherapy	Radical radiotherapy & HT	Hormone Therapy	Active monitoring	Watchful waiting	Other local treatment
Policy 1 :Once at age 50	377	218	1	578	317	-19	465
Once at age 55	899	479	71	1312	782	-193	1016
Once at age 60	2222	1094	314	3007	1998	-870	2233
Once at age 65	3851	1757	817	5198	3382	-2110	3337
Once at age 70	420	1802	1234	7193	0	4606	3771

Starting screening later, stopping earlier - 4 yearly

	Radical prostatectomy	Radical radiotherapy	Radical radiotherapy & HT	Hormone Therapy	Active monitoring	Watchful waiting	Other local treatment
Policy 2 : Every 4 years from 50 - 74	7180	4888	1142	14938	5966	1079	9798
Every 4 years from 50 - 70	7071	4261	833	12184	5979	-708	8364
Every 4 years from 55- 74	7544	4782	1229	14081	6324	-282	9224
Every 4 years from 55 - 70	7454	4362	1030	12533	6364	-1334	8392

Starting screening later, stopping earlier - 2 yearly

	Radical prostatectomy	Radical radiotherapy	Radical radiotherapy & HT	Hormone Therapy	Active monitoring	Watchful waiting	Other local treatment
Policy 3 : Every 2 years from 50 - 74	9727	5796	935	16805	8227	-1162	11391
Every 2 years from 50 - 70	9543	5041	745	13525	8238	-3294	9597
Every 2 years from 55- 74	10086	5616	1014	15136	8650	-2746	10650
Every 2 years from 55 - 70	9948	5202	905	13880	8625	-3682	9824

Appendix K: Additional men affected by adverse effects of treatment for screening compared to no screening

Baseline policies 1-4

	Exess 30 day mortality RP	Sexual dysfunction	Urinary incontinence	Bowel complications
Policy 1 :Once at age 50	0.2	3405.8	71.0	33.8
Policy 2 : Every 4 years from 50 - 74	26.2	19831.8	1417.8	871.4
Policy 3 : Every 2 years from 50 - 74	37.2	23273.4	1866.7	988.9
Policy 4 : Every year from 50 - 74	40.6	25146.2	2118.0	1042.2

Screening once

	Exess 30 day mortality RP	Sexual dysfunction	Urinary incontinence	Bowel complications
Policy 1 :Once at age 50	0.2	3405.8	71.0	33.8
Once at age 55	0.0	4408.8	169.8	81.0
Once at age 60	11.3	6688.2	419.9	198.8
Once at age 65	19.5	9738.0	727.3	350.2
Once at age 70	2.5	8905.5	181.9	408.8

Starting screening later, stopping earlier - 4 yearly

	Exess 30 day mortality RP	Sexual dysfunction	Urinary incontinence	Bowel complications
Policy 2 : Every 4 years from 50 - 74	26.2	19831.8	1417.8	871.4
Every 4 years from 50 - 70	25.8	17488.1	1363.4	739.8
Every 4 years from 55- 74	27.3	19399.7	1474.2	861.3
Every 4 years from 55 - 70	26.7	18196.1	1435.9	774.1

Starting screening later, stopping earlier - 2 yearly

	Exess 30 day mortality RP	Sexual dysfunction	Urinary incontinence	Bowel complications
Policy 3 : Every 2 years from 50 - 74	37.2	23273.4	1866.7	988.9
Every 2 years from 50 - 70	36.6	20777.5	1798.2	848.2
Every 2 years from 55- 74	38.3	22402.0	1919.6	964.7
Every 2 years from 55 - 70	37.4	21401.5	1876.0	887.8

Appendix L: Incremental QALYS per man with cancer for screening compared to no screening

Policy	QALYS/per man with cancer	Discounted QALYs per man with cancer
Baseline screening options		
Policy 1 :Once at age 50	-0.04	-0.03
Policy 2 : Every 4 years from 50 - 74	-1.09	-0.61
Policy 3 : Every 2 years from 50 - 74	-1.28	-0.71
Policy 4 : Every year from 50 - 74	-1.37	-0.77
Screening once		
Policy 1 : Once at age 50	-0.04	-0.03
Age 55	-0.08	-0.05
Age 60	-0.19	-0.11
Age 65	-0.38	-0.21
Age 70	-0.50	-0.27
Screening later/shorter 4 yearly		
Policy 2 : Every 4 years from 50 - 74	-1.09	-0.61
Age 50-70	-0.89	-0.50
Age 55-74	-1.08	-0.59
Age 55-70	-0.95	-0.52
Screening later/shorter 2 yearly		
Policy 3 : Every 2 years from 50 - 74	-1.28	-0.71
Age 50-70	-1.06	-0.60
Age 55-74	-1.23	-0.68
Age 55-70	-1.11	-0.62

Appendix M: Additional resource use for screening compared to no screening

Resources required incremental to no screening - baseline policies 1 - 4

Policy		General Practice Nurse	PSA test	GP appoint-ment	Biopsy	Hospital admission (post biopsy)	Bone scan	CT scan	MRI scan	Outpatient attendance	RP	RT planning	RT fractions	HT (annual)	Dexa scan	Hormone refractory treatment	Terminal care	Other treatment for local
1	Screen	254,512	238,090	-26,847	12,276	57	0	0	0	17,433	0	0	0	0	0	0	0	0
	Treatment	81,917	118,759	-264	4,194	20	1,528	1,528	0	119,023	377	219	8,106	20,503	10,240	555	8	465
	Total	**336,430**	**356,849**	**-27,111**	**16,470**	**77**	**1,528**	**1,528**	**0**	**136,456**	**377**	**219**	**8,106**	**20,503**	**10,240**	**555**	**8**	**465**
2	Screen	1,492,802	1,016,718	-145,233	257,160	1,197	-1,546	0	-1,546	348,684	0	0	0	0	0	0	0	0
	Treatment	989,158	1,733,164	70,999	57,749	269	23,541	23,541	0	1,662,164	7,180	6,025	222,917	247,793	123,645	2,804	-951	9,783
	Total	**2,481,959**	**2,749,881**	**-74,233**	**314,910**	**1,465**	**21,995**	**23,541**	**-1,546**	**2,010,848**	**7,180**	**6,025**	**222,917**	**247,793**	**123,645**	**2,804**	**-951**	**9,783**
3	Screen	2,981,019	3,475,855	11,307	588,536	2,739	-2,413	0	-2,413	840,485	0	0	0	0	0	0	0	0
	Treatment	1,087,052	2,130,121	24,205	81,659	380	27,409	27,409	0	2,105,916	9,727	6,726	248,854	272,359	135,882	2,836	-1,011	11,365
	Total	**4,068,071**	**5,605,976**	**35,512**	**670,195**	**3,119**	**24,997**	**27,409**	**-2,413**	**2,946,401**	**9,727**	**6,726**	**248,854**	**272,359**	**135,882**	**2,836**	**-1,011**	**11,365**
4	Screen	6,022,125	7,521,835	394,458	1,269,612	5,908	-2,566	0	-2,566	1,859,588	0	0	0	0	0	0	0	0
	Treatment	1,120,079	2,371,326	-14,226	98,918	460	28,437	28,437	0	2,385,553	11,171	7,073	261,701	280,649	140,010	2,804	-1,045	11,975
	Total	**7,142,204**	**9,893,161**	**380,231**	**1,368,530**	**6,369**	**25,871**	**28,437**	**-2,566**	**4,245,141**	**11,171**	**7,073**	**261,701**	**280,649**	**140,010**	**2,804**	**-1,045**	**11,975**

Note Screen includes screening and diagnosis, treatment includes monitoring

Resources required incremental to no screening- screening once at ages 55, 60, 65, 70

Policy		General Practice Nurse	PSA test	GP appoint-ment	Biopsy	Hospital admission (post biopsy)	Bone scan	CT scan	MRI scan	Outpatient attendance	RP	RT planning	RT fractions	HT (annual)	Dexa scan	Hormone refractory treatment	Terminal care	Other treatment for local
Age 55	Screening	221,576	180,501	-55,591	18,800	87	0	0	0	25,691	0	0	0	0	0	0	0	0
	Treatment	173,307	257,100	-2,635	9,387	44	3,220	3,220	0	259,734	899	550	20,348	43,380	21,663	412	-221	1,016
	Total	**394,883**	**437,601**	**-58,226**	**28,187**	**131**	**3,220**	**3,220**	**0**	**285,425**	**899**	**550**	**20,348**	**43,380**	**21,663**	**412**	**-221**	**1,016**
Age 60	Screening	180,900	-94,216	-88,988	26,143	122	-637	0	-637	32,513	0	0	0	0	0	0	0	0
	Treatment	324,215	494,730	-13,906	18,715	87	6,632	6,632	0	508,636	2,222	1,408	52,080	81,158	40,527	1,220	-391	2,233
	Total	**505,115**	**400,515**	**-102,894**	**44,858**	**209**	**5,995**	**6,632**	**-637**	**541,149**	**2,222**	**1,408**	**52,080**	**81,158**	**40,527**	**1,220**	**-391**	**2,233**
Age 65	Screening	142,010	36,523	-110,839	25,467	119	705	0	705	24,810	0	0	0	0	0	0	0	0
	Treatment	416,777	665,371	-36,972	26,889	125	8,650	8,650	0	702,342	3,851	2,572	95,180	104,373	52,097	1,331	-518	3,337
	Total	**558,787**	**701,894**	**-147,811**	**52,356**	**244**	**9,355**	**8,650**	**705**	**727,152**	**3,851**	**2,572**	**95,180**	**104,373**	**52,097**	**1,331**	**-518**	**3,337**
Age 70	Screening	122,316	30,491	-95,314	30,296	141	2,574	0	2,574	27,862	0	0	0	0	0	0	0	0
	Treatment	451,027	526,416	148,942	0	0	8,134	8,134	0	377,474	420	3,034	112,264	112,955	56,378	1,679	-569	3,760
	Total	**573,343**	**556,908**	**53,628**	**30,296**	**141**	**10,707**	**8,134**	**2,574**	**405,336**	**420**	**3,034**	**112,264**	**112,955**	**56,378**	**1,679**	**-569**	**3,760**

Note Screen includes screening and diagnosis, treatment includes monitoring

Resources required incremental to no screening- starting screening later/stopping earlier than baseline policies - 4 yearly screening

Policy		General Practice Nurse	PSA test	GP appoint-ment	Biopsy	Hospital admission (post biopsy)	Bone scan	CT scan	MRI scan	Outpatient attendance	RP	RT planning	RT fractions	HT (annual)	Dexa scan	Hormone refractory treatment	Terminal care	Other treatment for local
Age 50-70	Screening	1,322,884	1,282,099	-176,522	191,027	889	0	0	0	256,345	0	0	0	0	0	0	0	0
	Treatment	900,839	1,603,644	30,338	57,684	268	20,870	20,870	0	1,573,306	7,071	5,091	188,373	225,630	112,605	2,392	-1,045	8,356
	Total	**2,223,723**	**2,885,743**	**-146,184**	**248,711**	**1,157**	**20,870**	**20,870**	**0**	**1,829,651**	**7,071**	**5,091**	**188,373**	**225,630**	**112,605**	**2,392**	**-1,045**	**8,356**
Age 55-74	Screening	1,169,786	695,173	-142,007	256,991	1,196	1,223	0	1,223	349,888	0	0	0	0	0	0	0	0
	Treatment	955,472	1,682,138	44,732	58,299	271	22,460	22,460	0	1,637,406	7,544	6,007	222,261	239,343	119,434	2,313	-1,121	9,191
	Total	**2,125,257**	**2,377,311**	**-97,275**	**315,290**	**1,467**	**23,683**	**22,460**	**1,223**	**1,987,294**	**7,544**	**6,007**	**222,261**	**239,343**	**119,434**	**2,313**	**-1,121**	**9,191**
Age 55-70	Screening	1,008,240	955,989	-175,230	179,843	837	849	0	849	237,976	0	0	0	0	0	0	0	0
	Treatment	894,656	1,597,699	14,500	59,013	275	20,645	20,645	0	1,583,199	7,454	5,389	199,405	224,084	111,832	2,139	-1,104	8,377
	Total	**1,902,896**	**2,553,688**	**-160,730**	**238,856**	**1,112**	**21,494**	**20,645**	**849**	**1,821,175**	**7,454**	**5,389**	**199,405**	**224,084**	**111,832**	**2,139**	**-1,104**	**8,377**

Note Screen includes screening and diagnosis, treatment includes monitoring

Resources required incremental to no screening- starting screening later/stopping earlier than baseline policies - 2 yearly screening

Policy		General Practice Nurse	PSA test	GP appoint-ment	Biopsy	Hospital admission (post biopsy)	Bone scan	CT scan	MRI scan	Outpatient attendance	RP	RT planning	RT fractions	HT (annual)	Dexa scan	Hormone refractory treatment	Terminal care	Other treatment for local
Age 50-70	Screening	2,628,990	2,923,906	-67,540	443,123	2,062	0	0	0	629,839	0	0	0	0	0	0	0	0
	Treatment	985,880	1,978,421	-29,070	82,338	383	23,908	23,908	0	2,007,491	9,543	5,783	213,956	246,961	123,235	2,123	-1,164	9,586
	Total	**3,614,870**	**4,902,327**	**-96,610**	**525,462**	**2,445**	**23,908**	**23,908**	**0**	**2,637,330**	**9,543**	**5,783**	**213,956**	**246,961**	**123,235**	**2,123**	**-1,164**	**9,586**
Age 55-74	Screening	2,333,890	1,826,403	15,231	579,076	2,695	730	0	730	828,289	0	0	0	0	0	0	0	0
	Treatment	1,031,728	2,044,681	-15,083	82,632	385	25,243	25,243	0	2,059,764	10,086	6,625	245,137	258,479	128,966	2,265	-1,206	10,621
	Total	**3,365,618**	**3,871,084**	**148**	**661,708**	**3,079**	**25,974**	**25,243**	**730**	**2,888,053**	**10,086**	**6,625**	**245,137**	**258,479**	**128,966**	**2,265**	**-1,206**	**10,621**
Age 55-70	Screening	1,983,802	2,254,441	-69,382	423,346	1,970	476	0	476	598,339	0	0	0	0	0	0	0	0
	Treatment	983,057	1,962,657	-43,568	82,533	384	23,982	23,982	0	2,006,225	9,948	6,104	225,855	246,253	122,882	2,281	-1,155	9,806
	Total	**2,966,859**	**4,217,098**	**-112,950**	**505,879**	**2,354**	**24,458**	**23,982**	**476**	**2,604,564**	**9,948**	**6,104**	**225,855**	**246,253**	**122,882**	**2,281**	**-1,155**	**9,806**

Note Screen includes screening and diagnosis, treatment includes monitoring

Appendix N: Additional costs for screening compared to no screening

Incremental costs screening to no screening - baseline policies 1 - 4

Policy		General Practice Nurse	PSA test	GP appoint-ment	Biopsy	Hospital admiss. (post biopsy)	Bone scan	CT scan	MRI scan	Outpatient attendance	RP	RT planning	RT fractions	HT (annual)	Dexa scan	Hormone refractory treatment	Terminal care	Total Cost (£million)	Discounted total cost (£million)
1	Screen	3.00	2.44	-1.04	3.77	0.14	0.00	0.00	0.00	2.38	0.00	0.00	0.00	0.00	0.00	0.00	0.00	10.70	11.86
	Treatment	0.99	0.00	-0.01	1.29	0.05	0.26	0.18	0.00	16.50	2.51	0.16	1.66	22.57	0.81	4.39	0.04	51.40	37.16
	Total	**4.00**	**2.44**	**-1.05**	**5.06**	**0.19**	**0.26**	**0.18**	**0.00**	**18.88**	**2.51**	**0.16**	**1.66**	**22.57**	**0.81**	**4.39**	**0.04**	**62.10**	**49.02**
2	Screen	17.62	13.11	-5.61	79.06	2.92	-0.27	0.00	-0.33	47.53	0.00	0.00	0.00	0.00	0.00	0.00	0.00	154.03	106.78
	Treatment	12.09	0.79	2.74	17.75	0.66	4.07	2.70	0.00	231.44	48.00	4.22	42.64	274.69	9.88	22.18	-4.10	669.76	348.49
	Total	**29.72**	**13.89**	**-2.87**	**96.81**	**3.58**	**3.80**	**2.70**	**-0.33**	**278.96**	**48.00**	**4.22**	**42.64**	**274.69**	**9.88**	**22.18**	**-4.10**	**823.79**	**455.27**
3	Screen	35.19	29.15	0.44	180.93	6.69	-0.42	0.00	-0.51	114.56	0.00	0.00	0.00	0.00	0.00	0.00	0.00	366.03	242.93
	Treatment	13.40	0.27	0.94	25.10	0.93	4.74	3.14	0.00	293.46	64.94	4.79	48.39	304.40	10.94	22.43	-4.36	793.51	422.19
	Total	**48.59**	**29.41**	**1.37**	**206.04**	**7.62**	**4.32**	**3.14**	**-0.51**	**408.02**	**64.94**	**4.79**	**48.39**	**304.40**	**10.94**	**22.43**	**-4.36**	**1,159.54**	**665.13**
4	Screen	71.10	62.62	15.24	390.31	14.43	-0.44	0.00	-0.54	253.47	0.00	0.00	0.00	0.00	0.00	0.00	0.00	806.18	523.04
	Treatment	13.88	-0.16	-0.55	30.41	1.12	4.92	3.26	0.00	332.44	74.56	5.05	51.00	315.29	11.33	22.18	-4.50	860.23	464.82
	Total	**84.97**	**62.47**	**14.69**	**420.72**	**15.55**	**4.47**	**3.26**	**-0.54**	**585.90**	**74.56**	**5.05**	**51.00**	**315.29**	**11.33**	**22.18**	**-4.50**	**1,666.42**	**987.86**

Note Screen includes screening and diagnosis, treatment includes monitoring

Incremental costs screening to no screening- screening once at ages 55, 60, 65, 70

Policy		General Practice Nurse	PSA test	GP appoint-ment	Biopsy	Hospital admiss. (post biopsy)	Bone scan	CT scan	MRI scan	Outpatient attendance	RP	RT planning	RT fractions	HT (3 monthly)	Dexa scan	Hormone refractory treatment	Terminal care	Total Cost (£million)	Discounted total cost
Age 55	Screen	2.62	1.71	-2.15	5.78	0.21	0.00	0.00	0.00	3.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	11.68	12.19
	Treatment	2.10	-0.03	-0.10	2.89	0.11	0.56	0.37	0.00	36.00	6.00	0.39	3.97	47.70	1.72	3.26	-0.95	103.98	66.19
	Total	**4.72**	**1.68**	**-2.25**	**8.67**	**0.32**	**0.56**	**0.37**	**0.00**	**39.51**	**6.00**	**0.39**	**3.97**	**47.70**	**1.72**	**3.26**	**-0.95**	**115.66**	**78.38**
Age 60	Screen	2.14	0.83	-3.44	8.04	0.30	-0.11	0.00	-0.13	4.43	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.05	12.17
	Treatment	3.92	-0.15	-0.54	5.75	0.21	1.15	0.76	0.00	70.53	14.87	0.96	9.73	88.98	3.20	9.65	-1.68	207.34	113.23
	Total	**6.06**	**0.68**	**-3.98**	**13.79**	**0.51**	**1.04**	**0.76**	**-0.13**	**74.96**	**14.87**	**0.96**	**9.73**	**88.98**	**3.20**	**9.65**	**-1.68**	**219.39**	**125.40**
Age 65	Screen	1.68	0.13	-4.28	7.83	0.29	0.12	0.00	0.15	3.38	0.00	0.00	0.00	0.00	0.00	0.00	0.00	9.29	8.86
	Treatment	5.06	-0.41	-1.43	8.27	0.31	1.50	0.99	0.00	97.66	25.69	1.70	17.14	114.94	4.13	10.52	-2.23	283.84	136.95
	Total	**6.74**	**-0.28**	**-5.71**	**16.10**	**0.59**	**1.62**	**0.99**	**0.15**	**101.04**	**25.69**	**1.70**	**17.14**	**114.94**	**4.13**	**10.52**	**-2.23**	**293.13**	**145.81**
Age 70	Screen	1.44	0.03	-3.68	9.31	0.34	0.45	0.00	0.54	3.80	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.23	8.09
	Treatment	5.43	1.65	5.75	0.00	0.00	1.41	0.93	0.00	52.60	2.90	1.98	20.01	123.36	4.44	13.28	-2.45	231.29	95.23
	Total	**6.88**	**1.68**	**2.07**	**9.31**	**0.34**	**1.85**	**0.93**	**0.54**	**56.40**	**2.90**	**1.98**	**20.01**	**123.36**	**4.44**	**13.28**	**-2.45**	**243.53**	**103.32**

Note Screen includes screening and diagnosis, treatment includes monitoring

Incremental costs screening to no screening- starting screening later/stopping earlier than baseline policies - 4 yearly screening

Policy		General Practice Nurse	PSA test	GP appoint-ment	Biopsy	Hospital admiss. (post biopsy)	Bone scan	CT scan	MRI scan	Outpatient attendance	RP	RT planning	RT fractions	HT (3 monthly)	Dexa scan	Hormone refractory treatment	Terminal care	Total Cost (£million)	Discounted total cost
Age 50-70	Screen	15.62	11.34	-6.82	58.73	2.17	0.00	0.00	0.00	34.94	0.00	0.00	0.00	0.00	0.00	0.00	0.00	115.98	87.84
	Treatment	11.03	0.34	1.17	17.73	0.66	3.61	2.39	0.00	219.00	47.24	3.58	36.21	250.38	9.01	18.92	-4.50	616.75	326.89
	Total	**26.64**	**11.68**	**-5.65**	**76.46**	**2.83**	**3.61**	**2.39**	**0.00**	**253.94**	**47.24**	**3.58**	**36.21**	**250.38**	**9.01**	**18.92**	**-4.50**	**732.73**	**414.73**
Age 55-74	Screen	13.81	9.56	-5.49	79.01	2.92	0.21	0.00	0.26	47.69	0.00	0.00	0.00	0.00	0.00	0.00	0.00	147.97	92.10
	Treatment	11.68	0.49	1.73	17.92	0.66	3.88	2.57	0.00	228.03	50.40	4.17	42.15	265.38	9.54	18.29	-4.83	652.10	328.81
	Total	**25.49**	**10.06**	**-3.76**	**96.93**	**3.58**	**4.10**	**2.57**	**0.26**	**275.72**	**50.40**	**4.17**	**42.15**	**265.38**	**9.54**	**18.29**	**-4.83**	**800.07**	**420.91**
Age 55-70	Screen	11.90	7.94	-6.77	55.29	2.04	0.15	0.00	0.18	32.44	0.00	0.00	0.00	0.00	0.00	0.00	0.00	103.17	74.21
	Treatment	10.95	0.16	0.56	18.14	0.67	3.57	2.37	0.00	220.41	49.81	3.75	37.89	248.62	8.94	16.91	-4.76	617.98	317.65
	Total	**22.85**	**8.10**	**-6.21**	**73.43**	**2.71**	**3.72**	**2.37**	**0.18**	**252.85**	**49.81**	**3.75**	**37.89**	**248.62**	**8.94**	**16.91**	**-4.76**	**721.15**	**391.85**

Note Screen includes screening and diagnosis, treatment includes monitoring

Incremental costs screening to no screening- starting screening later/stopping earlier than baseline policies - 2 yearly screening

Policy		General Practice Nurse	PSA test	GP appoint-ment	Biopsy	Hospital admiss. (post biopsy)	Bone scan	CT scan	MRI scan	Outpatient attendance	RP	RT planning	RT fractions	HT (3 monthly)	Dexa scan	Hormone refractory treatment	Terminal care	Total Cost (£million)	Discounted total cost
Age 50-70	Screen	31.04	25.37	-2.61	136.23	5.04	0.00	0.00	0.00	85.85	0.00	0.00	0.00	0.00	0.00	0.00	0.00	280.91	202.28
	Treatment	12.16	-0.32	-1.12	25.31	0.94	4.14	2.74	0.00	279.57	63.70	4.11	41.52	276.23	9.93	16.79	-5.01	730.67	394.40
	Total	**43.20**	**25.05**	**-3.73**	**161.54**	**5.97**	**4.14**	**2.74**	**0.00**	**365.42**	**63.70**	**4.11**	**41.52**	**276.23**	**9.93**	**16.79**	**-5.01**	**1,011.58**	**596.68**
Age 55-74	Screen	27.55	22.07	0.59	178.02	6.58	0.13	0.00	0.15	112.90	0.00	0.00	0.00	0.00	0.00	0.00	0.00	348.00	210.39
	Treatment	12.71	-0.17	-0.58	25.40	0.94	4.37	2.89	0.00	286.95	67.35	4.67	47.21	288.64	10.38	17.92	-5.20	763.49	393.49
	Total	**40.26**	**21.91**	**0.01**	**203.43**	**7.52**	**4.49**	**2.89**	**0.15**	**399.85**	**67.35**	**4.67**	**47.21**	**288.64**	**10.38**	**17.92**	**-5.20**	**1,111.48**	**603.87**
Age 55-70	Screen	23.42	18.32	-2.68	130.15	4.81	0.08	0.00	0.10	81.56	0.00	0.00	0.00	0.00	0.00	0.00	0.00	255.75	170.37
	Treatment	12.10	-0.48	-1.68	25.37	0.94	4.15	2.75	0.00	279.36	66.43	4.30	43.45	274.89	9.88	18.04	-4.98	734.52	382.59
	Total	**35.52**	**17.83**	**-4.36**	**155.52**	**5.75**	**4.23**	**2.75**	**0.10**	**360.91**	**66.43**	**4.30**	**43.45**	**274.89**	**9.88**	**18.04**	**-4.98**	**990.27**	**552.95**

Note Screen includes screening and diagnosis, treatment includes monitoring

Appendix O: Probabilistic sensitivity analysis

Parameter		Mean	Std dev	95th Percentile	
				Low	High
Lifetime probability of Pca	Background	0.10	0.00	0.09	0.10
	Policy 2	0.16	0.00	0.15	0.16
Proportion of people screen detected with PCa who would have died of other causes (Overdetection)		0.46	0.03	0.42	0.50
Mean lead time for PCs diagnosis in overdetected cases (yrs)		11.74	0.45	11.00	12.50
Mean lead time for PCa diagnosis in potentially relevant cases (yrs)		11.35	0.43	10.48	11.92
Relative rate of Pca death (50-74yrs)		0.87	0.05	0.77	0.95
Relative rate of Pca death (50+ yrs)		0.94	0.03	0.89	0.97
PCa age specific incidence (Background)	50-54	0.41	0.06	0.31	0.51
	55-59	1.02	0.10	0.86	1.19
	60-64	2.27	0.18	2.01	2.59
	65-69	4.24	0.29	3.82	4.77
	70-74	6.45	0.35	5.92	7.05
	75-79	7.89	0.37	7.30	8.49
	80-84	8.01	0.52	7.18	8.88
	85+	6.81	0.60	5.73	7.69
PCa age specific incidence (Policy 2)	50-54	3.87	0.45	3.12	4.61
	55-59	4.18	0.23	3.81	4.53
	60-64	6.64	0.31	6.15	7.15
	65-69	9.13	0.46	8.44	9.92
	70-74	15.22	0.94	13.41	16.50
	75-79	2.40	0.23	2.01	2.76
	80-84	2.64	0.37	1.96	3.14
	85+	2.36	0.42	1.61	2.96
PCa age specific mortality (Background)	50-54	0.01	0.01	0.00	0.02
	55-59	0.04	0.02	0.02	0.07
	60-64	0.13	0.03	0.08	0.19
	65-69	0.38	0.06	0.28	0.49
	70-74	0.97	0.11	0.79	1.15
	75-79	2.13	0.21	1.78	2.47
	80-84	4.05	0.37	3.43	4.64
	85+	7.17	0.53	6.35	8.08

Parameter		Mean	Std dev	95th Percentile	
				Low	High
Pca age specific mortality (Policy 2)	50-54	0.01	0.01	0.00	0.02
	55-59	0.03	0.01	0.01	0.06
	60-64	0.11	0.03	0.07	0.17
	65-69	0.33	0.06	0.24	0.43
	70-74	0.86	0.11	0.69	1.04
	75-79	1.93	0.20	1.63	2.26
	80-84	3.79	0.35	3.21	4.35
	85+	7.11	0.53	6.28	8.00
Discounted total cost		£ 437.74	£ 19.29	£ 417.84	£ 461.86
Discounted QALYs		-49264	4246	-54096	-42696
Discounted QALYs per man with		-0.61	0.05	-0.67	-0.53
Radical prostatectomy		6603	327	6319	6970
Radical radiotherapy		4594	275	4256	4916
Radical radiotherapy & HT		1218	309	824	1817
Hormone Therapy		15341	1231	13626	17137
Active monitoring		5303	319	4965	5726
Watchful waiting		1211	371	566	1789
Other local treatment		1421	18	1398	1450
Exess 30 day mortality RP		24	1	23	26
Sexual dysfunction		19020	991	17994	20089
Urinary incontinence		1310	63	1259	1377
Bowel complications		837	47	777	887