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1 ABSTRACT

As early prostate cancer is often asymptomatic, the disease is often not diagnosed until it has reached an advanced, incurable stage. However, if diagnosed when it is still confined to the prostate, prostate cancer is potentially curable. At present, there are no completed prospective evaluations or other scientific evidence to suggest that prostate cancer mortality is reduced or that quality of life is increased either by curative treatment or by screening programmes. However, the potential effects of a screening programme can be modelled using decision analytic computer software.

The aim of this project was to develop a model for comparing the expected quality-adjusted life expectancy for a group of men subjected to a programme of screening for prostate cancer to that of a control group with conventional case-finding, given limited empirical data on the effectiveness of both strategies.

Due to limitations of existing data, the analysis was developed during the early stages of evaluating a prostatic cancer screening programme. We wish to illustrate how an analytic tool such as this model can be used in the future.

The model was functionally separated into two parts. The first part, the observation submodel, covers the first 6 years of the programme and classifies the screened population into different quality of life states, based on observed outcomes. The second part, the simulation submodel, predicts quality adjusted life-years for healthy participants and for prostate cancer patients who receiving curative treatment or expectant management. Data for the model were obtained from a pilot programme on screening for prostatic cancer in which a randomly selected population sample has been screened by digital rectal examination in Norrköping Sweden in 1987 and 1990. The outcome evaluated in the model was quality-adjusted life expectancy for individuals in the cohort invited to the screening programme, compared to results for population controls.

While the preliminary results identify some health benefits associated with screening, more accurate empirical data for a number of key variables could improve the evaluation. One feature of this model is that it combines solid, empirical data from the observation submodel with simulated results. When better empirical data on the actual consequences of different strategies are available, they can easily be analysed by using this model.
2 INTRODUCTION

2.1 Prostate cancer

Prostate cancer is the most common malignancy among men in Sweden, and is the leading cause of death from cancer in males. In 1989 the age-adjusted incidence in Sweden was 102.2 cases/year per 100 000 males. The incidence has risen over the last 20 years with an annual increase of 1.2% (Socialstyrelsen, 1992). The increase in age-adjusted incidence may reflect more extensive use of diagnostic procedures in an aging population not dying from other illnesses. As an effect of an aging population, the annual increase in prevalence is expected to continue. This should lead to increasing health care costs.

As early prostate cancer is often asymptomatic, it may not diagnosed until it has reached an advanced, incurable stage. However, prostate cancer diagnosed when it is still confined to the prostate is potentially curable. Consequently, an effective screening programme combined with effective curative treatment should reduce the mortality rate.

At present there is no scientific evidence to suggest that prostate cancer mortality is reduced, or that quality of life is increased by potentially curative treatment or by screening programmes (Pedersen, 1993). Outcome data from large randomized trials of screening and treatment strategies will not be available for 15 or 20 years. Until then, we must use methods which combine available data on effects and costs of prostate cancer screening programmes with estimations of the long-term consequences of various treatment approaches.

2.2 Tools for evaluation

Clinical decisions in health care are often made under conditions of uncertainty. The uncertainty results from errors in clinical data, ambiguity and variations in interpretation of data, uncertainty concerning relations between clinical diagnostic data and true presence of the disease and uncertainty about the effects of treatment (Weinstein & Fineberg, 1980). Another factor which has become increasingly important in the decision making process is the patient’s preferences for treatment. Medical professionals are trained to handle the uncertainty by virtue of their education and experience. Doctors are becoming used to balancing the risks against potential benefits for the individual patient. In certain decision situations, clinical experience and intuitive calculations of risks and benefits could suffice, but in complex circumstances formal calculations are needed.
Decision analysis is a systematic approach to decision making under conditions of uncertainty. It differs from traditional clinical decision making in several ways. The process is explicit and quantitative, forcing the decision maker to define the logical structure of the problem and to use empirical data systematically. One advantage of formally structuring the problem is that clinical controversies and existing gaps in clinical evidence are brought to light. Formal decision making primarily facilitates policy making at a group level, but may also indirectly assist doctors in making decisions for individual patients.

The decision tree is an analytic tool which displays the temporal sequence of all relevant components in a decision analytic problem. The tree contains of two types of nodes; decision nodes and chance nodes, each of which is followed by two or more alternatives (branches or paths). The decision node represents a point where the decision makers can elect one of several alternative actions. The chance node represents a point at which one of several events beyond the control of the decision maker takes place. The chance node denotes the possibility of the occurrence of an event. All paths end in an outcome, e.g., good health or death. By multiplying the probabilities for all events along the alternative paths, the probability for a specific final outcome can be estimated. When the value of each possible outcome is quantified (e.g. as monetary costs or life-years), the expected value for each alternative can be estimated in the same analysis.

For creating the tree and for performing attendant calculations, one of several available computer software packages (e.g. SMLTREE, Decision-maker) may be used. It allows the analyst to change the structure of the tree easily and to test the robustness of the outcome by changing the probabilities at various chance nodes using other figures (sensitivity analysis). This technique is especially useful in complex decision problems involving uncertain data e.g. when evaluating an emerging technology. Prostate cancer screening is one example of a "changing technology", for which new data are continually presented. The analytic tools must therefore be flexible. At the beginning of a technology's life-cycle, the result of the analysis is associated with uncertainty, but later, when the model is validated and new data are available, the result becomes more reliable.

A more complex model could include various types of simulation of events. Since the quality of the simulation depends strongly on the supporting data, the result of a simulation (e.g. of the quality adjusted life years gained by prostate cancer screening) may be quite inaccurate. Nevertheless a simulation model is a useful tool for sensitivity analyses. With a good user interface the educational potential of a simulation model is considerable. Instead of reading text or diagrams, a user can perform experiments with the model, and may then focus on situations of particular interest. The user is forced to consider and interpret the
results based on his/her own experience and thereby develops an intuitive knowledge of the programme studied.

This report is written to describe the design of a decision tree modelling results of prostate screening. The model was generated using SMLTREE, DOS based decision making software program (Hollenberg, 1986).

The purpose of this work was to develop a decision analytic model which:
* graphically displayed the screening-, diagnosis- and treatment process
* compared the expected quality adjusted life years in a group of men subjected to a screening programme or conventional case-finding. The outcome evaluated in the model was quality adjusted life expectancy for an individual in the population invited to the screening programme.
* facilitated performance of sensitivity analysis of key variables and key probabilities in the preliminary model.

2.3 The Norrköping screening study

The very few decision models on prostatic cancer screening are based on data extracted from the literature (Thompson et al). Models based on various clinical and epidemiological studies from different countries and health care systems, conducted with different methodologies, may suffer from bias and other methodological problems. The effectiveness of screening programmes is very sensitive to local circumstances and is therefore especially difficult to evaluate by synthesizing the literature. In the case of prostatic cancer screening, conditions vary widely among countries with different cultural settings. The structure of the health care system, the willingness of the population to participate in prevention programmes, and the prevalence of the disease are issues with great potential impact on the effectiveness of the programme. All of these factors contribute to make prostatic screening extremely complex and difficult to assess.

In order to prevent or at least reduce some of these problems we have based our analysis mainly on one pilot study in a randomly selected group of Swedish men. Data for the model were obtained from a prospective prostate cancer screening study performed in Norrköping, Sweden (Pedersen et al, 1989; Varenhorst et al, 1992).

In 1987, 1494 men were randomly selected from the total male population of 9026 men aged 50-69 living in the municipality of Norrköping in southern Sweden. The remaining 7532 served as a control group. The men in the experimental group were invited to partake
the first screening round in 1987. If they still lived in the area, they were also sent a personal invitation to take part in the second screening in 1990. 114 of the original population were lost due death or having left the area between the screening rounds. Furthermore, 13 men with cancer diagnosed at the first screening, and 4 men with cancer diagnosed during the interval between screening rounds were not invited to participate in the second round. Some 78% of the original invited population attended the first round and 70% of those were invited to the 2nd round. Thus 83% of the original invited group participated in at least one of the two screening rounds.
3 CONSTRUCTION OF THE MODEL

The model can be functionally separated into two parts. The first part, called the observation submodel, includes the first N years of the programme and mainly distributes the participants of the screening programme to different health states. The second part, called the simulation submodel, estimates quality adjusted life years for healthy participants, and for patients with prostate cancer detected during the rest of the study period.

Figure 1. A description of the model.

![Diagram](image)

As we currently have only had data from two screening rounds in the pilot study, we have restricted the observation model to data for a 3 year period\(^1\). When the observation period is extended, the observation submodel can be extended and the uncertainty in the total model can be reduced.

3.1 The observation submodel

The tree structure for the observation submodel describes the screening-, diagnosis- and treatment process, (Appendix 1). The probabilities displayed in the tree are mainly calculated from the results of the Norrköping screening programme. For example: Of the 1494 men were invited to the screening (INVJ), 1163 attended the screening (SATTJ) and 331 did not (SNATTJ). This makes the probability for SATTJ equal to 0.7784 (1163/1494) and the probability for SNATTJ equal to 0.2216 (331/1494).

\(^1\)The population at risk in the programme was planned to be screened every third year.
The tree structure was originally developed for a detailed cost calculation model (Carlsson et al, 1992) and is therefore somewhat more extensive than is necessary for the current analysis. Calculations of quality-adjusted life years were based on having classified study participants into different health states. This did not require dividing subjects into different cancer stages categories (advanced, localised cancer) or categories of treatment (surgery/irradiation). However, in order to clarify the model, we describe the first part to reflect the outcome for the patients in the pilot study. Data from both the intervention group and the control group were analysed.

3.1.1 Data collection, intervention group

Data in distribution model were mainly extracted from the pilot study and published in earlier reports (Pedersen et al, 1990; Varenhorst et al, 1992; Carlsson et al, 1992). The decision tree for the intervention group starts with the invitation to all potential participants for the first screening round (INV1). Some of the potential participants attended the screening (SATT1), some did not (SNATT1) (see Appendix 1). Of those who attended, some screened positive by digital rectal examination (DRE) performed by a general practitioner or urologist (SPOS1). They were offered biopsy examination. Some underwent the biopsy (BATT) and some did not (BNATT). The biopsies were either positive (BPOS1) or negative (BNEG). The patients with positive biopsies were treated for prostate cancer (CANC) according to cancer type (ADVANC/LOC) (see below). Among patients with negative biopsies, some subsequently developed an "interval" cancer (IPOSa and on) after some time. The biopsy negative patients, who did not develop "interval" cancer (INEGa), attended the second screening round (ATT). None of them screened positive (NEG).

However most men were negative at the initial screening (SNEG). Some of them later developed an "interval" cancer (IPOSb). These lesions were diagnosed by biopsy examination (BIOPb and on), or were detected by histological examination of tissue removed at transurethral resection of the prostate (TURP) presumably performed for benign prostatic hyperplasia (TURPb and on). According to cancer type and quality of life state, they were assigned to a state in the simulation submodel.

Some of those who attended the first screening round screened negative and did not develop an "interval" cancer (INEGb). These patients were not invited to the second screening round (DROPOUT). They had either died (DIEa) or had moved from the health care district (LIVEa) before the second screening round.
Of those invited to screening round 2 (NOc), most attended the screening (SATT2b). Some screened positive, and later also had cancer confirmed at biopsy (BPOSb and on). They were treated for cancer and transferred to the quality of life model in the same way as described above. Of those who were screening negative in round 2 (SNEGb), some later developed "interval" cancers (IPOSb), detected by biopsy examination (BIOPb) or by examination of tissue removed at transurethral resection of prostate (TURPb). Other men who did not attend the second screening round later developed an "interval" cancer (IPOSd), detected by biopsy examination (BIOPd) or at transurethral resection of the prostate (TURPd).

There also were a number of men who didn't attend the first screening round (NATT1) who did present at the second screening round (ATT2). A few screening positive (SPOSc), had a positive biopsy (BPOS2) and were treated for cancer. They were placed in the model according to their cancer stage, as described above. Of those who neither participated in the first nor the second round (NATT2), some developed an interval cancer (IPOSd), detected at biopsy examination (BIOPe) or transurethral resection of prostate (TURPe). They then entered the simulation model. Some declined participation in the whole screening programme. In the model, different proportions classified as either alive (LIVEb) or dead (DIEb) based on data from official life-tables (SCB, 1991).

Each diagnosed cancer had been classified as localized (LOC) or advanced (ADVANC) after examination at hospital. If the cancer was localized, one of four treatment alternatives was chosen: surgical treatment (SURG), surgical as well as radiation treatment (SURG+RAD), radiation treatment alone (RAD) or expectant management (EXPECT). If the cancer was advanced, the patients were distributed to different treatments according to the probabilities in the branch (outAD) shown in Appendix 1. The outcomes (distribution on health states) from the treatment alternatives were assumed to be the same in the model (outLO). The outcome from expectant management has its own distribution on health states (outLE).

Each time the subtree CANC was used, the probabilities pADV and pLOC were assigned their unique values, as were the probabilities pSRG, pSRGRAD, pRAD and pEXP. The probabilities were taken from the outcomes of the Norrköping screening programme and a follow-up study on all patients treated of prostatic cancer at the Department of Urology at University Hospital in Linköping between 1985 and 1988 (Pedersen et al, 1992).

To determine the probabilities with which cancer patients would enter the different health states (q1AD, q2AD, q3AD, q4AD, q5AD, dieAD for advanced cancer, q1LO, q2LO,
9

q3LO, q4LO, q5LO, dieLO for localized cancer with curative treatment and q1LE, q2LE, q3LE, q4LE, q5LE, dieLE for localized cancer with no primary curative treatment), results from an inquiry to a panel of urologists presented below were used.

3.1.2 Data collection, control group

The observation model for the control group includes data from a 3 year period. First the population was distributed into those with suspected cancer (SUSPCA) and those without any sign of cancer (NOSUSP) in that period. Even without a screening programme, many men are examined for prostate cancer as a part of ordinary health check-ups or as a consequence of surgery for benign prostatic hyperplasia.

We assumed that all men with suspected cancer were examined by fine-needle biopsy, and that some were found to have cancer (POS) while the rest were not (NEG). The cancer cases (CANC) were classified as clinically localized (LOCAL) or clinically advanced (ADVANC) based on data in the Norrköping study.

The subgroup with advanced cancer was then distributed into 5 health states and a death state based on the same principles as in the intervention group. Before the patients with localized cancer were distributed into health states, they were assigned different treatment strategies (SURG, SURG+RAD, RAD or EXPECT).

The majority of men in the control group without any sign of cancer (NEG) were divided into LIVEb and DIEb. The probability of surviving (LIVEb) was calculated from the official lifetables statistics in the following way \((1-pDIE[60]) \times (1-DIE[61]) \times (1-pDIE[62])\). The NOSUSP group were distributed into LIVEc and DIEc according to the same principles.

3. 2 The simulation submodel

This part of the model uses a Markov process approach (Beck, 1983), which calculates the remaining lifetime after the observation period for all subjects included in the screening programme. The purpose is to estimate the change in lifetime and quality of life after the screening and cancer treatment.
The submodel calculates quality adjusted life years for men 60\(^2\) year old with prostatic cancer with or without primary curative treatment, as well as for participants who did not attend the programme and those who had a true negative result at the screening examination. In this submodel all subjects were distributed into 6 health states the first year.

Regarding classification of health states with different quality of life, discussions may arise about which aspects of life should be considered in the quality of life concept, and how to represent them quantitatively. In our model we have divided the decline from a healthy state to death into 6 states. From the 32 health states in an original matrix presented by Rosser and Kind (1978) we selected the following representative 6 health states for prostatic cancer.

1) Minimal if any social disability or suffering from disease, reducing the ability to perform some spare time activities. The patient may have mild pain or psychological disturbance relieved with mild medication (salicylate or diazepam preparations).

2) Disability and pain of a moderate degree. The individual is too diseased to work and/or has serious trouble maintaining a normal social life. He is only able to perform limited domestic work and has pain and/or psychological disturbance which do not disappear with mild medication.

3) Moderate disability and severe pain. The individual is too diseased to work and/or has serious trouble maintaining a normal social life. He is only able to perform limited domestic work. He has pain that requires heavy analgesia (e.g. morphine).

4) Mostly wheelchair-bound or bedridden, with pain of a moderate degree. The individual has pain and psychological disturbances which do not disappear with mild medication (salicylate or diazepam preparations).

5) Mostly wheelchair-bound or bedridden and with severe pain. Pain and/or psychological disturbances require heavy analgesia (e.g. morphine).

6) Dead.

The only transitions considered were those involving movement from a less serious health state to a more serious health state. In the end of the analysis period, all subjects would

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\(2\) The average age in the cohort in the pilot study the year when the first screening round was performed.
have died so that the total number of quality-adjusted life years generated could be calculated.

3.2.1 Inquiry regarding survival and morbidity

In order to generate data on the distribution of patients into different health states in the model, a panel of urologists was engaged. The panel consisted of twelve Swedish urologists, at eight different university hospitals and county hospitals.

They were asked:
"Based on your clinical experience and medical literature we want you to give your opinion how 100 patients in each of following categories would be distributed in 6 states including death for each year, during a period of 20 years. When you have neither experience nor support from literature, we want you to make assumptions."

1) Clinically advanced cancer not still confined to the prostate. Often this type of cancer is beyond cure.

2) Clinically localized cancer still confined to the prostate, with a size, growth rate or other characteristic making it advisable to treat it.

3) Clinically localized cancer suitable for expectant management. The cancer is still confined to the prostate, but some circumstances make treatment inadvisable. The patient can be considered too old, the cancer can be considered too small or to have a too low growth rate.

Below the questions were tables with the rows containing the six quality of life states as described above, and the columns containing the years 1 to 20.

The details of the inquiry are presented in Appendix 2. The answers indicated relative large variations among the panelists.

3) Departments of Urology in Linköping, Jönköping, Västerås, Göteborg, Örebro, Malmö, Norrköping and Lund.
Figure 2: Cumulative mortality for different categories of patients with prostatic cancer.

The results in the figure are consistent with data recently published by Johansson et al., 1992, demonstrating that there is a rather small expected effect of potentially curative treatment of clinically localised prostatic cancer, relative to outcomes expected in similar patients not receiving curative treatment.

In order to illustrate the distribution of patients into different health states, we present the data from the panelists for patients with advanced cancer (figure 3). The figures for patients with localized cancer with and without curative treatment are presented in Appendix 3.
3.2.2 Utility measure for different health states

To allow adjustments for differences in quality of life in different health states we primarily used the figures based on British data derived using a psychometric approach (Rosser & Kind, 1978). In order to do a sensitivity analysis we used Swedish data from a small pilot study in which the time trade-off method (Weinstein & Fineberg, 1980) was used to estimate utilities for the same states (Levin et al, 1991).

Table 1. Utility measures for different health states.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.986</td>
<td>0.887</td>
</tr>
<tr>
<td>2</td>
<td>0.900</td>
<td>0.512</td>
</tr>
<tr>
<td>3</td>
<td>0.870</td>
<td>0.255</td>
</tr>
<tr>
<td>4</td>
<td>0.680</td>
<td>0.517</td>
</tr>
<tr>
<td>5</td>
<td>0.000</td>
<td>0.200</td>
</tr>
<tr>
<td>Dead*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The quality of life coefficient for death was set at 0.
The differences between the Swedish and British utility data may reflect differences in utility assessment methods, as well as the small sample sizes in both studies.

3.2.3 Expected survival in the healthy population

To estimate the survival in the healthy population, we used the official statistics on expected survival in different ages for men (SCB, 1990). According to Swedish vital statistics from 1987, prostate cancer accounts for only about 4% of cause-specific mortality for men above 65 years of age (Dödsorsaker, 1987).
4 COMBINING THE SUBMODELS

4.1 "Initiation QALYs"

Combining the two parts of the model requires certain caveats. The screening activities in the distribution model actually occurred over the course of three years. Thus the complete model would have to consist of one branch that is totally evaluated during the first step. In the second and later steps, evaluation of the model was achieved in SMLTREE by setting only the probability of inviting the participants to the screening to 1, while the probabilities of entering the quality of life states directly were set to 0. Therefore, the only way of getting to the ALIVE quality of life state and the cancer quality of life states is through the screening activities.

By constructing the model this way, we distributed properly the participants to the different states. However, since the first step (i.e., evaluation of results of screening) takes three years, the contributions based on only one life year would have been too low. To compensate for this, the quality adjusted life years for the first three years were calculated separately and added as a "initiation QALY", summarizing 3 years' experience as a single utility value (Hollenberg, 1986). Then before all the calculations were performed, these life years were added to the cumulated sum of life years in the model. The quality of life of each branch was determined and then multiplied by the probability of being in that branch.

This technique was also used for validating the model (see 4.4). Since the death rate table summation begins at the same age as in the model including the screening part (i.e., 63 years), the first three years of normal death rates had to be calculated as an "initiation utility".

4.1.1 Contribution of QALYs in the intervention group

The short term observation model summarizes the experience in the first 3 years as a single step. All participants with false positive examinations at the first screening round (SPOS1) were considered "alive" - shorthand for screening negative - and were therefore transported to the ALIVE state in the simulation model. All these participants contributed 3 years of full quality of life (QALYs) during the time period between the screening rounds. The ones with "interval" cancer were considered to have contributed 1.5 years of full quality of life, and 1.5 years according to their subsequent quality of life state (see below). The ones with cancer diagnosed at screening contributed 3 years according to their quality of life state.
The dropouts, i.e. men who were impossible to reach at screening round 2, were considered to have contributed 1.5 years with full quality of life if they were assumed to have died. The other dropouts were treated like all the others who did not have a cancer at the first screening round or in the interval between the screening rounds - since they did not have cancer at this time period, they contributed 3 years of full quality of life.

Those who never participated in the whole screening programme were considered to have been subject to normal mortality rates. They were assumed to have contributed 3 years of full quality of life.

Those who were found to have cancer at screening round 2 were immediately (i.e. in the same year), transferred to the simulation model. Their quality of life was calculated according to their cancer type and the expected corresponding health state.

4.1.2 Contribution of QALYs in the control group

Those who have had a cancer detected contributed 1.5 years with full health plus 1.5 years where the average quality of life for the health states possibly for men with cancer were used as an approximation. The men without any sign of cancer (LIVEb or LIVEc) contributed 3 years of full health. It was assumed that those who died did so after 1.5 years, and therefore contributed 1.5 years full health. The live group was handled in a manner analogous to those in the intervention group.

4.2 Initiation

Patients were initially assigned to the different quality of life states by the observation model (Figure 1). The states associated with cancer (q1**..q5**) are filled from the cancer treatment submodel according to results for the second year in the inquiry. Some of the patients reached the DEATH state this way.

Live participants who had not had prostate cancer diagnosed reached the ALIVE state. The rest of the participants reached the state DEATH through the branches INV1, SATT1, SNEG, INEGb and DROPOUT. Even though these branches only seem to incorporate those who attended screening round 1, all subjects who died from causes other than cancer are included in DEATH in this branch.
4.3 Yearly transitions between states

When running the model for the remaining lifetimes of the participants, the probability of departure from the ALIVE state is estimated according to a table of age-specific mortality rates (SCB, 1990) (see Appendix 4). To minimize unnecessary computation work probabilities for death over the age of 110 are set to 1.

The probabilities of being in various health states were modelled according to the physician panel inquiry. The only transitions considered in the model are the ones from various health states to death, and the probabilities are based on formulas derived from the different tables. While not modelled here, there would be successive transitions from cancer states with high quality of life to states with lower quality. There would also be possible transitions from lower quality of life states to higher ones (e.g. after successful treatment) as well as transitions which occur more rapidly than on a year to year basis. Without data on which transitions really occurred, we chose to model the numbers of patients in the states as declining or constant according to some simple formulas presented below.

4.3.1 Advanced cancer

The states of advanced cancer can be fairly well described as exponential functions in early years. They fits well into the modelling concept provided by SMLTREE in that a given percentage of the patients in each state moved to another state at each time step.

The formulas used to describe the transitions were generated by using least squares regression. A straight line was fitted to the number pairs (x, log(y)) where x is the year and y the number of patients in the state. By re-exponentiating, the coefficients of the formula \( y = b \cdot a^x \) were found. One problem with this was that some places in the table had the value zero, which is not allowed as input to the logarithm. Another problem was that the values close to zero probably had lower precision. That made the exponential formula unnecessary well fitted to the last years at the expense of the model fitting for the first years. Both problems were solved by omitting the least squares equation from the last 10 years from the inquiry which had been based on up to 20 years of observation.

The coefficient b was changed to fit the model which began with 100% healthy, rather than basing it on the inquiry, which began with 100% diseased in year 0.
4.3.2 Localized cancer

The states of localized cancer with or without curative treatment were somewhat more difficult to model. From the inquiry it was obvious that the state with the highest quality of life would fit well to a straight line. The other states were becoming commoner for several years before the number of individuals were declining. Many of the states were not empty after 20 years.

To minimize complexity, we decided to model all states as straight lines, that is, \( y = k \times x + m \), where the coefficients were identified with the least squares method. Some lines had a small positive slope \( k \), which, in SMLTREE, indicated that a probability larger than 1.0 was found. Therefore, when a line had a positive slope, the slope was set to zero and the mean of all annual values was used as intercept \( m \).

SMLTREE cannot model straight line declining probabilities, since this requires a probability that changes for each step. This problem can be solved in different ways. We chose to use the formula shown in Appendix 5.

Actually, both the slope \( k \) and the intercept \( m \) were changed to correct for the fact that the inquiry assumes that 100% of patients are diseased in year 0, while the model assumes that 100% are healthy in year 0. Extrapolation of the line in the inquiry determined when no patients were left in the state. This was used to construct a slope for a line between the initial value from the model and the time when no patients were left.

4.4 Validation of the model

For checking the results, one can compare the remaining life years from the model with data from the published mortality statistics. Using only the death rate table in a straightforward manner by summing survival probabilities for each year in the model, the results differs from published rates by exactly 0.5 years because the yearbook statistics are based on calculations at mid-year (the "half year problem"). To make the result from the model consistent with the published data, 0.5 years are added as a tail utility for the state DEAD. Thus, after all the calculations are performed, 0.5 life years are added to the cumulated sum of life years in the model.
5 RESULTS

5.1 Preliminary simulation based on actual data in the Norrköping study

When the model was run based on screening data from digital rectal examination screening (in Appendix 1) and the British utility data to adjust the quality of life for different health states, the estimated expected quality adjusted survival for the 60 year old men in the intervention group were 18.72724. With an observation model based on data from the unscreened control group, the 60 year old man would expect to live 18.62940 years instead. It is difficult to interpret these results for several reasons. The uncertainty surrounding the calculations is unknown, and it is difficult to interpret the figures in an analysis limited to cancers detected during the first six-year period of the programme.

Assuming that the difference of 0.09784 QALYs is real, it may have minimal importance for a single individual. However one way to appreciate the implication of the magnitude of the difference in expected number of QALYs is to multiply the difference by 860 000, which is representing the approximate number of men at risk (50-69 years) in Sweden. If a programme with DRE screening, including 2 rounds, were implemented in Sweden, a gain of 0.09784 QALYs for each individual would result in a total gain for that cohort of 84 000 QALYs.

5.2 Sensitivity analysis

To highlight the uncertainty of the results. a number of sensitivity analysis were performed. In table 2 the results from some of the analyses based on other input data are presented as expected numbers of QALYs.
Table 2. Number of expected QALYs for a 63 year old man with or without screening based on different assumptions.

<table>
<thead>
<tr>
<th>Various utilities</th>
<th>QALYs</th>
<th>Gain or loss in QALYs with screening compared to without</th>
</tr>
</thead>
<tbody>
<tr>
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<td>18.72724</td>
<td>+0.069784</td>
</tr>
<tr>
<td>Swedish</td>
<td>18.69926</td>
<td>+0.06986</td>
</tr>
</tbody>
</table>

Results for this intervention group, compared to results for alternative screening and treatment strategies presented by Gustavsson et al, 1992:

**Gustavsson et al**
1. DRE; all localized Ca curative treated 18.72251 +0.09311
2. DRE; only Ca < T2A treated 18.57256 -0.05684
3. DRE+TRUS+PSA; all localized Ca treated 18.81923 +0.18983
4. DRE+TRU+PSA; only Ca < T2A treated 18.51829 -0.11111

*A pilot study performed at Södersjukhuset in Stockholm including 2400 randomly selected men.

**Stage T2A includes cancer without extension beyond the prostate capsule in which the tumor volume is less than half of the lobe.

Table 2 shows that the choice of utility data play a relative small role, compared to the choice of screening or treatment strategies. The alternative from Gustavsson et al which is most similar to the one in the Norrköping study is (1) DRE as single method with treatment of all localized cancers detected. The Norrköping data and data from Södersjukhuset when DRE is single method result in a small difference in number of QALYs. When we compare Norrköping data with outcome of a more sensitive strategy (DRE+TRUS+PSA) the number of expected QALYs 1.5 higher for the combined strategy. We may compare a progressive treatment policy with the more conservative management approach used in the study at Södersjukhuset, i.e. treatment of only cancers less than stage T2A. The gain in QALYs is higher with the DRE-screening and treatment policy in Linköping even if we assume the combination of all three screening methods are used as long as the conservative treatment policy is applied. This shows the importance of treatment policy and of course the efficiency of the treatment modalities. We need more data of the effectiveness of different treatment strategies before we are able to estimate the expected number of QALYs with accuracy. Until then we must use limited data and reasonable assumptions.
In earlier decision analysis of outcomes of prostate cancer screening the results are contradictory. Thompson et al found a small gain in quality adjusted survival by screening, while Mold et al which found a loss of 3.5 quality adjusted life-months for a 65-year man. Differences in the assumptions made in these two studies make comparisons of the results difficult.

Both studies were based on data from the literature. As some of the authors' assumptions differ from Swedish conditions it is impossible to draw conclusions for Sweden. Nevertheless these studies are good examples of a promising approach to tackle a complex decision problem which includes a number of difficult questions.

One problem concerns effectiveness of different strategies for management of localised prostatic cancer. Evaluation of the expected survival for patients with localised prostatic cancer is complicated for several reasons. One problem is that different Swedish urologists define patients "suitable for curative treatment" differently. Another problem is that data on survival after curative treatment of clinically localised prostatic cancer are lacking. An ongoing randomised clinical study on prostatectomy versus symptomdriven treatment for patients with localised cancer will provide some data on that by the end of this decade. However, we do not know if patients with prostatic cancer diagnosed in a screening programme differ with respect to tumour stage and life-expectancy from patients diagnosed without screening, or from patients treated under clinical trial conditions.

A larger number of localized otherwise undetectable cancers were found in the intervention group than in the control group as a consequence of the screening programme. This will underestimate the long run positive effect of screening. The magnitude of the underestimation is a consequence of how patients with otherwise undetected localized cancers will later present with advanced cancer. The current limitation of the pilot programme to two rounds will hopefully be less problematic in the future. The continuing pilot programme will include screening of the cohort in 1993 and a follow up of the total intervention group and the control group. This will provide us with important data which may be used in future versions of the model. Currently the model should be perceived as an important tool for describing and understanding the problems with assessing screening programmes for prostate cancer. Over time, when more accurate data are available, it can be used for calculating the effect in number of QALYs of different screening strategies, and may also illustrate the effect of screening compared to no screening.
The evaluation of prostate cancer screening by means of a decision analytic model cannot eliminate uncertainty, but can facilitate handling the uncertainty in a systematic way as in other screening programmes. The value of earlier detection of prostate cancer depends on the degree to which it permits more successful and/or less invasive treatment.


Pedersen KV. Localized carcinoma of the prostate. Aspects on screening, staging and surgical treatment (Diss.). Linköping University, 1993.


Appendix 2: Distribution submodel for the control group
Appendix 4: Distribution on health states
### Appendix 5: Inquiry tables

The tables below contain the averaged answers to the inquiry made of twelve Swedish physicians with experience in treating patients with prostate cancer.

The questions in the inquiry read (one question and Rosser matrix for each diagnosis) as follows.

*Based on your clinical experience and medical literature we want you to give your opinion of how 100 patients with the diagnosis

* advanced stage prostate cancer
* localized prostate cancer without treatment aimed to cure
* localized prostate cancer with treatment aimed to cure

would be distributed in the following quality of life states during a number of years (maximum of 20 years). Where you have neither personal experiences nor data from the literature, we want you to make assumptions."

#### Advanced stage prostate cancer

Percent of patients with advanced CaP each year in each quality of life state.

<table>
<thead>
<tr>
<th>Year</th>
<th>State 1</th>
<th>State 2</th>
<th>State 3</th>
<th>State 4</th>
<th>State 5</th>
<th>State 6</th>
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## Localized prostate cancer without treatment

Percent of patients with localized CaP without treatment each year in each quality of life state.

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## Localized prostate cancer with treatment

Percent of patients with localized prostate cancer with curative treatment each year in each quality of life state.

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<th>State 4</th>
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(Death rates used in the model.)

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Appendix 7: Formulas to estimate the transition probabilities from different health states to dead.

\[
\begin{align*}
Q1.AD[n+1] &= 0.7533 \times Q1.AD[n] \\
Q2.AD[n+1] &= 0.7497 \times Q2.AD[n] \\
Q3.AD[n+1] &= 0.7907 \times Q3.AD[n] \\
Q4.AD[n+1] &= 0.7804 \times Q4.AD[n] \\
Q5.AD[n+1] &= 0.7865 \times Q5.AD[n]
\end{align*}
\]

Exponential

\[
\begin{align*}
Q1.LO[n+1] &= \text{MAX}(0, 1-4369E-7/Q1.LO[n]) \times Q1.LO[n] \\
Q2.LO[n+1] &= \text{MAX}(0, 1-1400E-7/Q2.LO[n]) \times Q2.LO[n] \\
Q3.LO[n+1] &= \text{MAX}(0, 1-3600E-7/Q3.LO[n]) \times Q3.LO[n] \\
Q4.LO[n+1] &= 1.0000 \times Q4.LO[n] \\
Q5.LO[n+1] &= 1.0000 \times Q5.LO[n]
\end{align*}
\]

Line

\[
\begin{align*}
Q1.LE[n+1] &= \text{MAX}(0, 1-2222E-7/Q1.LE[n]) \times Q1.LE[n] \\
Q2.LE[n+1] &= \text{MAX}(0, 1-6500E-7/Q2.LE[n]) \times Q2.LE[n] \\
Q3.LE[n+1] &= \text{MAX}(0, 1-1500E-7/Q3.LE[n]) \times Q3.LE[n] \\
Q4.LE[n+1] &= 1.0000 \times Q4.LE[n] \\
Q5.LE[n+1] &= 1.0000 \times Q5.LE[n]
\end{align*}
\]

Constant

DEAD [n+1] = DEAD[n]
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