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Economic evaluation of screening for prostate cancer: a randomized population based programme during a 10-year period in Sweden

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Abstract

Prostate cancer is a growing health problem representing considerable costs. Screening and early curative treatment may reduce morbidity and possibly prevent future escalating costs. However, population screening programmes are generally not well accepted at present due to uncerainty about whether screening for prostate cancer can result in reduced mortality. Evidence from large, randomized, controlled trials is still lacking. The objective of this study was to calculate clinical and economic consequences of general prostate cancer screening based on a limited screening trial in a Swedish community and a decision-tree model. A random selection of 1492 men (50–69 years) were invited to repeated screening in 1987. They have been examined every third year (four rounds). The other 7679 men in the population act as controls. The results show that the total incremental health care costs for prostate cacer will increase by 179 million SEK per year with screening compared to no-screening. The number of detected cases of localized cancer will increase by about 1000, which represents an additional cost of about 158000 SEK per case. In conclusion, general screening for prostate cancer can be performed with a reasonable cost per detected localized cancer. Information on the long-term effect on life quality and cancer mortality is unknown.

Keywords: Prostate cancer; Screening; Economic evaluation; Decision model

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1. Introduction

1.1. Prostate cancer: a growing health problem

Prostate cancer is an age-related disease with a steadily increasing incidence. During the past 20 years the number of cases in Sweden has grown by an average of 1.5% per year [1]. We have calculated that the total health care costs for prostate cancer in Sweden have risen from approximately 500 million SEK in the mid 1980s to 770 million SEK 8 years later [2]. The increased use of methods such as the prostate specific antigen (PSA) for early detection, in combination with the fact that the disease becomes more common in the growing group of older men in our society, is indicative of a continued increase in costs during the latter part of the 1990s and the beginning of the 2000s. Furthermore, the increased use of potentially curative therapy for localized prostate cancer, and more expensive endocrine therapy for additional indications in advanced malignant disease, will also contribute to a rise in the demand for health care resources. Potentially curative therapy, radical prostatectomy or radiation therapy, which is initiated at an early stage can, in theory, cure the disease. This strategy requires an effective programme for diagnosing the tumours at an early stage. Prostate cancer has been the object of intensive research in order to attain better results in its care and management. Despite progress in the management of this disease, few areas in medicine generate greater disagreement, and this is certainly the case regarding screening for early detection of prostate cancer [3].

1.2. Screening: a controversial issue

Limited screening programmes to detect prostate cancer at an early stage have been conducted in several European countries. There is already large-scale, routine screening, especially in the US. On the basis of existing documentation up until now, various national Health Technology Assessment agencies and professional organizations have drawn divergent conclusions. The American Urological Association, the American Cancer Society [4,5] and the German Urology Association recommend general prostate screening, while the National Cancer Institute [6] and the Swedish Council on Technology Assessment in Health Care [7] point out the lack of scientific support for large-scale routine screening and advise against it. So-called opportunistic screening using digital rectal palpation, DRE and the PSA test continue to a greater and greater extent, however, when experts give conflicting signals.

Several other groups that have recently examined the literature recommend that large, randomized studies should be carried out at an appropriate point in time [8]. Keeping in mind that these studies will require follow-up for 10–15 years before reliable results are available concerning the cost-effectiveness of the screening programme, it can be seen that screening for prostate cancer constitutes a scientific dilemma. Since the methodology for both diagnosis and treatment is constantly evolving, some researchers think that it will not be possible to evaluate prostate cancer screening in the same way as was done, for example, with mammography.

For the present, we must refer to limited trials and analysis models in order to learn more about the costs and effects of prostate cancer screening. This study contains an economic evaluation of a limited trial with repeated screening for prostate cancer in a defined population in Sweden in the age group 50–69 years. Changes which took place in screening methodology during the screening period (1987–1996) were taken into consideration in the design of the programme and in how it has been conducted. The cost-effectiveness of the programme and the economic consequences of introducing a similiar programme throughout the whole country have been calculated based on a limited trial.

2. Materials and methods

Calculations of the intermediate cost-effectiveness of screening are based solely on our study of repeated prostate screening in Norrköping that started in 1987. For an analysis of the economic consequences for health care of introducing routine prostate screening, the data from the Norrköping study are supplemented with a medical records cost study published elsewhere [2], and relevant information from current literature.

2.1. Prostate cancer screening in Norrköping

During the first half of the 1980s, complications related to radical prostatectomy could be substantially reduced by means of improved operative techniques. The possibility of curing prostate cancer that was detected early thereby increased, and there was growing interest in screening. The politicians in Östergötland's county council decided to support a research project on prostate screening. At the start of the study, DRE was the only established screening method for early cancer detection. The PSA-test was not considered to be adequately evaluated and established as a diagnostic method for prostate cancer until the third screening in 1993, when it was included in the programme. Because of the time-adapted choice of methodology, the evaluation is of a 'moving target' character, i.e. the programme is based on accepted clinical practice at each time-point and it changes over time when the study is underway.

In 1987, 1492 men in central Norrköping were randomly selected from 9171 men available in the age group 50–69 years and were invited to participate in a screening study. The remaining 7679 men constituted the control group. The age distribution in both groups is uniform and representative of Sweden as a whole. The original study group was invited to participate in repeat screenings, at 3-year intervals, from 1987 to 1996 (Table 1). Those men in whom prostate cancer was detected at a screening or during the intervening time between screenings were excluded from further examination. In addition, there is a natural dropout due to moving away from the area or death. A total of four screening rounds were done. The control group was followed in the cancer registry during the same time period, and cases of prostate cancer were registered. The research ethics committee approved the study.

Results from rounds 1 to 3 have been reported earlier [9,10]. All remaining men irrespective of age were included in these evaluations. In the present study, calculations have been restricted to only those men who were 50–69 years of age at the time of the particular screening, accordingly the selected study group with respect to age risk. This is the population that would most likely be the target for routine screening in the future.

The rate of participation in the first screening round was 77.8%. In the second round the rate dropped to 70% in both age groups, and then increased to 73.1% in the third round and finally ended up at 73.8% in the fourth round, where only men younger than 70 years were invited to participate.

During the first screening, rectal palpation was the screening method used. In order to determine possible differences in findings by specialists and general practitioners, both general practitioners and urologists carried out the examination. In the second round DRE was done only by general practitioners. In the third and fourth screenings a blood sample was first obtained for a PSA-test, and then the general practitioner did DRE. During the whole study period, fine-needle aspiration biopsy was performed when there was a suspicion of prostate cancer because of positive DRE and or PSA >4 μg/l. Thereafter the patients were treated according to local praxis at each time-point.

2.2. Calculation of costs

Costs for different services are based on a medical record study. The costs for particular measures in the screening, diagnosis and management of prostate cancer patients are shown in Tables 2 and 3.

Table 4 shows the mean accumulated costs for prostate cancer from time of diagnosis to death divided according to stage and primary treatment. The costs were calculated for the course of the disease, and all treatment measures were

Table 1
Number of invited and participating men in the study group and in the control group at each round

Age	Screening 1 1987	Screening 2 1990	Screening 3 1993	Screening 4 1996
Study group				
Invited				
>50	1492	1363	1210	604[a]
50–69	1492	1162	852	604[a]
Participants				
>50	1161	957	895	446[a]
50–69	1161	811	623	446[a]
Control group				
50–69	7679	6196	4955	3758

[a]In the 4th screening (1996) only men younger than 70 years were invited.

Table 2
Costs related to measures in the screening programme (SEK, in 1996 prices)

Procedure	SEK
Digital rectal examination	144
PSA test	131
Fine-needle aspiration biopsy	1104

included. This information was used in the decision model to calculate the direct costs with and without screening.

2.3. Decision model analysis

According to Drummond et al. [11], an analytic procedure is to be preferred for making decisions about the distribution of resources in health care owing to three factors. (1) Without systematic analysis, it is difficult to identify clearly the relevant alternatives. (2) The viewpoint assumed in an analysis is important. (3) Without some attempt at measurement, the uncertainty surrounding orders of magnitude can be critical.

The above factors are very applicable to the decision concerning screening for prostate cancer. In this case an analysis model is necessary as a result of a number of factors. (1) The scientific basis involving the costs and outcomes is weak. It is unlikely that a large evaluation study will be conducted in Sweden in the coming years due to ethical concerns and cost factors. In this case an analytic procedure can constitute a surrogate, i.e. using a limited, randomized study we are able to

Table 3
Costs related to measures in the management of prostate cancer (SEK, in 1996 prices)

Procedures		SEK
Out patient care		
Urologist	Telephone call/minute	6.67
Nurse	Telephone call/minute	3.33
Urologist	Visit	900
Nurse	Visit	450
Scintigraphy	Examination	1310
Urine culture	Test	180
General practitioner	Visit	600
District nurse	Visit	300
Palliative radiation therapy	Six sessions	11 000
In patient care		
Hospital	Day	2576
Nursing home	Day	950

Source: Ref. [2].

Table 4
Mean accumulated costs for management of prostatic cancer in different patient groups according to stage and primary treatment (SEK in 1996 prices)

Stage	Primary treatment	SEK
Advanced cancer	Expectant management	76 800
	Palliative treatment	217 300
Localized cancer	Expectant management	65 000
	Curative treatment	138 400

construct a hypothetical, national screening programme. (2) The complexity of the screening programme is very high. Two alternatives are studied, screening and no-screening. The results show the differences present between the various alternatives, but also how a possible screening programme can be designed differently in order to be more effective. (3) Uncertainty about the effects of screening is one of the reasons opportunistic screening is done. To a certain extent, our study provides answers to different effects of prostate screening.

We chose to construct a decision-tree for each screening occasion, which results in a total of four different decision-trees. The two alternatives in each decision-tree are a situation with screening according to the Norrköping model, and no-screening. This version is the fourth generation of our model reported after the first round [9]. The TREEAGE software program is used for the analysis.

Each tree describes the screening, diagnosis and therapy processes as costs for the screening examinations and costs for each newly diagnosed case of cancer in the form of type of cancer and therapy. The control group represents the no-screening alternative, and costs for the cases of cancer which occurred in the group during the studied period were obtained in the same way.

3. Results

We begin by presenting the most important results from the Norrköping trial. Table 5 shows the number of newly detected cancers, the stages and primary therapy in the intervention group and the control group. In addition, the numbers of interval cancers detected in the interval between two screenings in the respective populations are shown.

The screening programme generates a larger number of cases of prostate cancer that are detected earlier than in the no-screening alternative. The probability that detected cases of cancer are localized and that therapy will be potentially curative is therefore larger in the screening alternative. Those cancers detected in the control group are more frequently advanced and lead less frequently to curative therapy.

The number of detected cancer cases per 1000 men shows that the screening programme results in more than double as many detected localized cases of cancer as in the no-screening alternative. There are three times as many cancer cases

Table 5
Numbers of detected cases of cancer distributed according to stages and primary therapy in the intervention group, and also expressed per 1000 men in each group, respectively

	Intervention group						Control group
	Cancer detected at screening				Interval cancer	Cancer per 1000 men	Cancer per 1000 men
	Round 1	Round 2	Round 3	Round 4			
Stage							
Advanced	1	1	1	1	12	10.7	8.9
Localized	12	4	6	5	8	23.5	10.2
Primary treatment							
Curative	11	2	2	3	1	12.7	4.2
Palliative	1	1	1	1	10	9.4	8.5
Expectant management	1	2	4	2	8	11.4	6.4

managed with potentially curative therapy per 1000 individuals with screening than with no-screening.

A double-tailed *t*-test was carried out on the data series number of detected cases of cancer, localized and advanced, and the number of cases with curative, palliative and expectant management at each screening. The *P*-value for detected cases of cancer was 0.013, and for advanced cases of cancer it was 0.35. For curative treated cancer the *P*-value was 0.066, for palliative management it was 0.161, and for expectant management it was 0.051. The number of detected localized cancer cases per 1000 men is greater in a statistical sense with screening ($P < 0.05$). On the other hand, there is no difference in the number of detected cases with advanced cancer. The difference in the number of cases with curative treatment and expectant management was close to being significant (0.066 and 0.051, respectively).

3.1. Cost-effectiveness analysis

On the basis of our trial it is possible to relate the direct cost to several intermediate outcome measures (Table 6). The high cost for DRE in the first screening is due to the fact that both general practitioners and urologists did the examination. The PSA test was not used until the third and fourth screenings. The costs are calculated per detected cancer and per curative treated cancer. In the absence of follow-up data concerning survival and quality of life, these are the best intermediate measures of cost-effectiveness available.

The total direct cost for the screening programme is 18600 SEK per detected cancer, and 49800 SEK per patient receiving a potentially curative treatment. The cost varies considerably in the different screenings. The high cost per curative managed cancer in screening 3 is partly explained by the introduction of the PSA test in the screening. However, the difference between screenings 3 and 4 involves only one case.

Table 6
Costs for different items in the screening programme and cost per detected cancer and per curative treated cancer (SEK, in 1996 prices)

Procedures	Screening round				Total
	1	2	3	4	
Digital rectal examination	334 400	116 800	89 700	64 200	605 100
PSA	–	–	81 600	58 400	140 000
Fine-needle aspiration biopsy	51 900	36 400	33 100	80 600	202 000
Total costs	386 300	153 200	204 400	203 200	947 100
Cost-effectiveness ratio					
Cost per detected cancer	20 300	15 300	15 700	22 600	18 600
Cost per curative treated patient	32 200	76 600	102 200	67 700	49 800

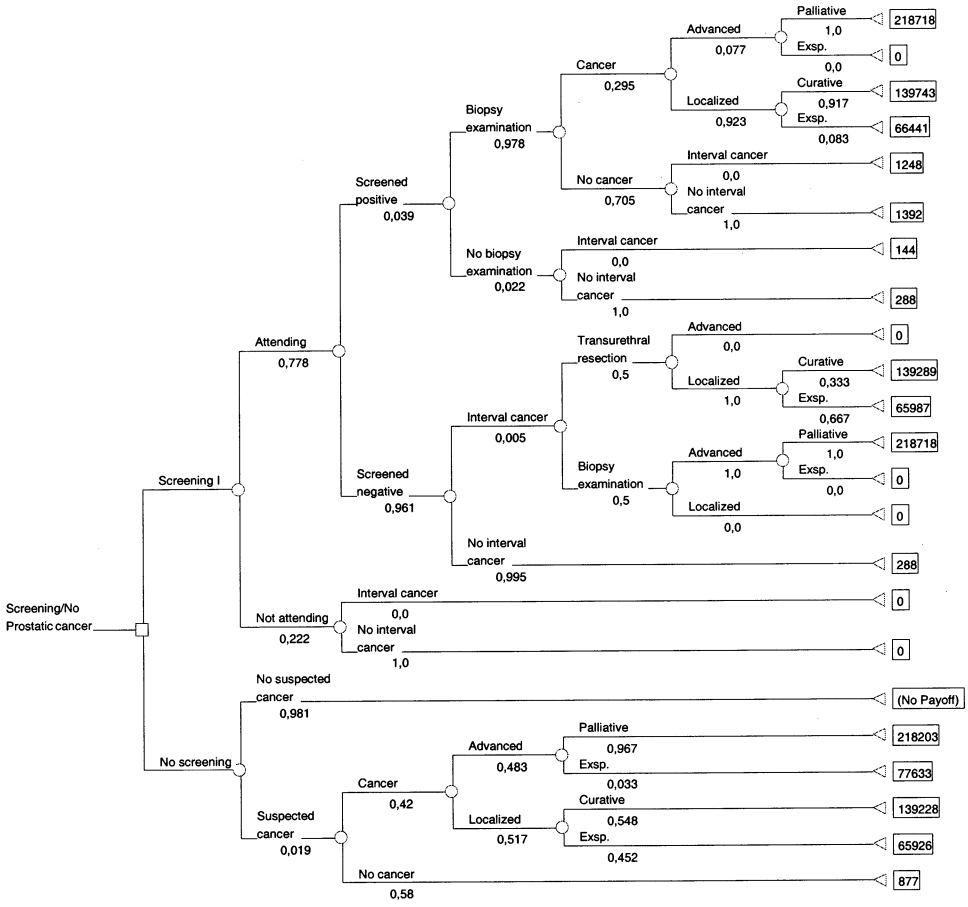

Fig. 1. Decision-tree for the first screening round.

3.2. Economic consequences of a general screening programme in Sweden

In order to illustrate the structure of the model, the decision-tree for the first screening round is shown in Fig. 1. Some of the key probabilities used in the decision-trees are reported in Table 7.

The decision-tree starts with the alternatives of offering screening or no-screening to men in the age group 50–69 years. The screening alternative involves those men who participate in the screening, and who are assessed after the examination as positive, suspicion of cancer, or negative, no suspicion of cancer. Suspicion of cancer leads to a fine-needle aspiration biopsy where a determination is made as to whether or not it is cancer. Where cancer is ascertained, either advanced or localized therapy follows according to the alternatives curative, palliative or expectant management. Among those individuals who are negative at the screening or who have been invited but have not participated in the screening, some develop

Table 7
Probabilities for different alternatives in the respective decision-trees in each round

	Screening round			
	1	2	3	4
Screening				
Scr.positive	0.039	0.041	0.043	0.166
Biopsy positive	0.295	0.161	0.292	0.085
Advanced	0.077	0.200	0.143	0.167
Localized	0.923	0.800	0.857	0.833
Advanced palliative	1.000	1.000	1.000	1.000
Localized curative	0.917	0.500	0.333	0.600
No-screening				
Suspected cancer	0.019	0.019	0.019	0.019
Cancer	0.420	0.235	0.467	0.437
Advanced	0.483	0.481	0.442	0.437
Localized	0.517	0.519	0.558	0.563
Advanced palliative	0.967	0.846	1.000	1.000
Localized curative	0.548	0.429	0.208	0.444

interval cancer. The structure of the no-screening alternative is similar. There are a number of individuals in the population in whom cancer is suspected. This suspicion arises in connection with other types of doctor's visits or health check-ups. Some of these are judged positive and cancer in an advanced/localized stage is ascertained. Therapy is offered according to the same alternatives as in the screening group. The number of cancer cases in the control group was obtained using the national cancer registry. The cost for examination of suspected cases of cancer is calculated to be an average of the two methods, fine-needle biopsy and transurethral resection, with microscopic examination of tissue from the prostate after transurethral resection for presumed benign enlargement of the prostate. The latter has occurred with interval cancer and in the control group.

Most probabilities used in the four different decision trees have on the whole been calculated using data from the screening programme in Norrköping and a few from the literature. To give an example, the probability of a suspicion of cancer in the 1st screening is 0.039 (45/1161), and the probability of no suspicion of cancer is 0.961 $(1 - 0.039)$.

Table 8
Cost-effectiveness ratio of the screening-programme when costs for treatment are included

	Screening round				
	1	2	3	4	Total
Cost per detected cancer	160 800	128 000	126 200	117 400	137 900
Cost per potentially curative treatment	254 600	639 900	820 100	352 300	370 100

Table 9
Incremental costs and detected cancers during a 12-year period with screening compared to no-screening for a cohort of men ages 50–69 years in Sweden

	Difference screening/no-screening	Per year	Per 1000 men and year
Costs (MSEK)	2150	179	0.19
Detected cancers			
Localized	12 850	1071	1.14
Curative treatment	8622	719	0.76
Advanced	750	63	0.067

Screening includes a total of four rounds, one every third year. Costs for screening and management of prostate cancer are included (1996 prices).

By using the model, we have calculated the total cost, including expected health care costs for prostate cancer for all cases, and distributed the total costs over detected cases of cancer that received potentially curative therapy in the respective groups. Furthermore the total cost for the programme has been distributed over the number of detected cancers in each screening and the number of cases that received potentially curative therapy (see Table 8).

With a general screening programme in Sweden based on the same principles as the Norrköping programme, costs for prostatic cancer are 4.9 milliard SEK (4.9×10^9 SEK) for 12 years (study period for cost estimations) or 411 million SEK per year. Even without screening, the same population will require substantial medical care resources for treatment of prostatic cancer. A comparison of incremental costs and detected cases of cancer for a general programme and the effects of no-screening is shown in Tables 9 and 10.

When we use our model to evaluate a general screening programme in Sweden for men ages 50–69 years we use the population in 1996, and the number of men at risk in the first screening will be 943000. The annual cost of a 12-year national screening programme compared to no-screening will be 179 million SEK. The cost per 1000 men at risk year will be 190000 SEK per year compared to the no-screening alternative.

The annual number of detected cancer cases with screening will exceed the no-screening alternative by approximately 1071 localized cancers, 719 of which have potentially curative treatment. If a general screening programme is carried out, 63 additional advanced cancers will be detected.

Table 10
Incremental cost with screening compared to no-screening

	Costs (SEK)
Cost per detected cancer	158 000
Cost per detected localized cancer	167 000
Cost per potentially curative treatment	249 000

If we distribute the excess costs generated by the screening programme over the additional cases of cancer detected (due to screening), we obtain a picture of the difference in costs per detected cancer with screening as compared to no-screening. The incremental cost per case receiving potentially curative treatment is 249000 SEK.

4. Discussion

Screening for prostate cancer is controversial, as it is associated with great uncertainty concerning a number of factors such as costs, the risk of overdiagnosing, and the negative effects of therapy [12,13]. We chose to calculate the effects of an actual screening programme for men in the age group 50–69 years during a 12-year period with a total of four screening occasions. The screening methods used were DRE and, in the last two rounds, the PSA-assay. Therefore the study has a 'moving target' character, since we chose to follow the current medical praxis at each time-point. We believe this approach is appropriate for evaluation in a field with important technological change.

The cost of the Norrköping screening programme itself distributed over the number of detected cancers is US$ 2268 (US$ 1 = 8.2 SEK), and per cancer case treated with potentially curative therapy it is US$ 6073. An American study by Kantrowitz et al. [14] demonstrates a cost of US$ 6012 (1995 prices) per detected cancer. The study was based on a screening programme at a company where 1219 men ages 50–65 participated. The screening examination consisted of DRE and the PSA test. Gustafsson et al. [15] studied the costs of six different screening strategies in a random selection of men in a defined population. Screening with DRE as the only method of examination resulted in a cost per detected cancer of US$ 3100 (direct cost to US$ 1875), and for curative managed patients it was US$ 4970 (direct cost to US$ 3000). A screening strategy that included PSA as the method of examination, and DRE if the PSA was >4 μg/l, resulted in a cost per detected cancer of US$ 3560 (direct cost to US$ 1855), and for curative managed patients the cost per detected cancer was US$ 5930 (direct cost to US$ 3092) (1993 prices). Indirect costs are also included in the cost calculations. Costs for screening in the different strategies are included in their study, but not treatment costs. Both these studies comprise only one screening round, which makes the figures not fully comparable with ours.

A general screening programme results in an additional cost (screening and therapy) of approximately US$ 23170 per 1000 men per year. The total cost for screening and the treatment thereafter, without any comparison with non-screening, is US$ 53659 per 1000 men per year. A corresponding calculation by Gustafsson et al. based on one screening indicates a cost the first year of US$ 74500 (US$ 45000 direct cost) per 1000 men screened with DRE only, and US$ 71200 (US$ 37100 direct cost) per 1000 men screened with PSA analysis followed by DRE on individuals with PSAs of 4 μg/l or more [15]. A Canadian study [16] on a screening

programme involving 671000 previously unscreened men aged 50–69 years using PSA as the screening method showed that the cost for the screening programme and treatment of detected cancers was estimated to be approximately US$ 52 million (1995 prices) per year over the first 10 years. Cost per year and per 1000 men screened was estimated at US$ 138000. It was estimated that re-screening the population would lead to decreased screening costs, and after 3 years the cost per 1000 men screened was estimated to be US$ 66000. An average cost over the first 10 years of screening and treatment for prostatic cancer was estimated to be approximately US$ 77000 per 1000 men screened. Optenberg and Thompson [8] evaluated different types of screening methods and subsequent treatment costs, and which consequences in the form of costs a screening programme would entail if carried out in the USA. Using DRE as the screening method led to a total cost of US$ 3.8 milliard (US$ 3.8×10^9) (1990 prices) in the first year. Allocated per 1000 men, the cost is approximately US$ 219000. Screening based on PSA (>4 μg/l) costs US$ 28 milliard (US$ 28×10^9) the first year. Allocated per 1000 men, the cost is approximately US$ 1.6 million (own calculations). In their study of different screening strategies and treatments for prostate cancer, Optenberg and Thompson found a substantially higher cost per 1000 men during the first year of a screening programme. The great difference in costs can be partially explained in that their study was limited to 1 year, and the treatment measures for prostate cancer in the USA are substantially higher than in Sweden.

Other studies show that several different screening methods have been used and that the research is relatively limited. Our study with repeated screening over a long period of time which includes both an intervention and a control group and which has a high rate of participation, is unique.

Screening programmes for the early detection of prostate cancer entail higher costs, and are also controversial because of uncertainty concerning the advantage of screening and the effectiveness of therapy. At present, the criteria for being able to carry out a national screening programme have not been fulfiled. However, research should be conducted on diagnostic methods, prevention, the natural history of the disease, and treatments, as well as on screening strategies. Toward this end, small-scale trials and modelling are recommended.

5. Conclusions

This study describes a decision model for screening for prostate cancer. Its major strength is that the model is based on an empirical database collected over several years of repeated screening with a study group and a control group. The 70–78% participation rate during four screening rounds is very high. The moving-target strategy reflects the reality of prostatic cancer management during a 12-year period. Based on the results of this study, we conclude that a decision-tree model is a suitable method for creating, on a scientific basis, a hypothetical but realistic national screening programme.

Our study shows that screening can be performed at a reasonable cost per detected localized cancer and probably at an acceptable cost per curative treated cancer. However, as long as knowledge is lacking about the long-term effects on quality of life and mortality, general screening can not be recommended. Limited studies such as the Norrköping trial are neccessary for testing different screening strategies, and the results can be used in modelling alternative scenarios as surrogates for large-scale, very costly and time consuming randomized trials.

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