A Cost Effectiveness Analysis of Cervical Cancer Screening in Sweden

Abstract The thesis deals with the problem of how to effectively minimize the prevalence of cervical cancer in Sweden. A cost effectiveness study with a societal perspective is undertaken comparing three alternatives: the current practice of organized cytological screening offered every third year, an alternative screening technology called liquid based cytology and finally a primary screening for HPV-DNA with a reflex test for cytology, using the LBC technique. The cost effectiveness is calculated through a markov cohort model. The results indicate that the LBC strategy is dominated by the HPV-DNA primary screening. The HPV-DNA screening is cost effective, leading to an incremental cost effectiveness ration of approximately 4700 SEK/Life Year gained. The conclusion is robust to univariate and multivariate sensitivity analysis. Hence, it is concluded that the initial investment in the new screening practice will lead to a large enough decline in incidence and mortality of cervical cancer, to be motivated from a societal point of view.

Tutor Magnus Johannesson

Authors Erik Dahlberg 19322

Viktoria Nilsson 19669

Contents

Glossary of Medical Terms

Biopsy Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body.

Cervical intraepithelial neoplasia (CIN) Grade of cellular change in the cervical cells, representing a continuum of histological changes ranging from well-differentiated CIN 1 (mild dysplasia), to severe dysplasia/carcinoma in situ, CIN 3.

Colposcopy The examination, therapy or surgery of the cervix and vagina by means of a specially designed endoscope introduced vaginally.

Conization The excision of a cone of tissue, especially of the cervix uteri.

Cytology screening Cytological method for diagnosing precancerous lesions of the cervix.

Incidence The number of new cases of a given disease during a given time period in a specified population. It is also used for the rate at which new events occur in a defined population.

Human Papillomavirus (HPV) A group of small non-enveloped DNA viruses infecting epithelia, sexually transmitted.

HPV DNA testing DNA probes specific for the identification of human papilloma virus.

Morbidity rate The proportion of patients with a particular disease during a given year per given unit of population.

Mortality rate All deaths reported in a given population due to a specific condition.

Liquid based cytology (LBC) An alternative method to the conventional Pap Smear technique when preparing cervical samples by producing a thin layer of cells on a slide.

Sensitivity The proportion of truly diseased person in a screened population who are identified as being diseased by the test. It is a measure of the probability of correctly diagnosing a condition for a specific test.

Specificity The proportion of truly nondiseased persons who are identified as such by the screening test. It is a measure of the probability of correctly identifying a nondiseased person for a specific test.

Papinicolaou smear (Pap smear) Collection of cell samples from the vagina, cervix, and cervical canal and spread on a glass slide.

Prevalence The total number of cases of a given disease in a specified population at a designated time.

ThinPrep Collection of cell samples using a special brush that is immediately washed in a special fluid. There is a possibility to conduct multiple tests (cytological and HPV-DNA) of the same liquid sample.

1 Introduction

Cervical cancer is one of the most prevalent forms of cancer among women globally. However, mortality rates in developed countries have declined in the recent decades.

Different strategies have been implemented worldwide to minimize the incidence and mortality by early detection of pre stages of the cancer defined as CIN1 and CIN2/3.

Sweden has been successful in decreasing the incidence of cervical cancer due to the introduction of a national screening program in the 1960's, from over 1000 women to 500 every year.("Cancer i siffor" Socialstyrelsen) Lately, however, this trend has leveled out. This raises the question whether the current screening practice is sufficient, or if there is a need to seek alternative methods for improving the screening outcome and further lower the incidence of cervical cancer.

A new testing technique, known as liquid based cytology (LBC), has been introduced in some countries. This technique could possibly improve the detection rate of women at risk of developing cervical cancer.

Others suggest that the discovered link between a sexually transmittable virus known as Human Papilloma Virus (HPV) and the development of the cellular abnormalities causing the cervical cancer, could be used to improve the screening outcome.

These two proposed alternative screening methods to the existing Swedish program would lead to higher intervention costs in the short run due to necessary investments, both in terms of new equipment and education of staff. However, in order to fully assess the effect of any change in the screening program a health economic analysis must be conducted in order to take into account the long term health and monetary implications, from a societal perspective.

The aim of this thesis is to answer the question whether any of the above mentioned changes in the cytological screening program would be cost effective from a health economic perspective. *In other words, would the initial investment in new screening practices lead to*

a further decline in the incidence and mortality of cervical cancer in Sweden to an extent that the investment is motivated, from a societal point of view?

In order to answer this question it is necessary to provide a contextual understanding of the various aspects of the disease and the treatment of cervical cancer. Hence, the thesis presents a general description of cervical cancer and its detection strategies. Thereafter, the theoretical foundations regarding health economic evaluation and the application of costing to the context of cervical cancer will follow. A systematic review of the published medical efficacy and economic studies on cervical cancer screening is also included. After that, the modeling and simulation of the natural history of cervical cancer by applying a dynamic Markov model will be presented, accompanied by the necessary assumptions. Finally, the results and sensitivity analysis of the cost effectiveness analysis will be presented. More detailed information concerning the design and input of the markov model can be found in the appendix.

Three strategies will be analyzed:

1. The current practice with cytological screening every third or fifth year as base case.
2. The substitution of conventional cytological sampling with Liquid Based Cytology (LBC), ceteris paribus.
3. Introducing LBC combined with HPV-DNA primary screening and cytological analysis as a triage method.

Note that the base case in any health economic evaluation should be no intervention at all, to avoid the trap of assuming that the current medical practice is already cost effective. However, screening for pre stages of cervical cancer has already been proven to not only be cost effective, but also lead to net savings due to a decrease in the long term treatment costs of cervical cancer. (Bistoletti et al 2005)

2 Cervical Cancer

2.1 Definitions and Diagnosis

History

In 1958, before the national screening program was initiated in Sweden, cervical cancer, was the third most common cancer form for women.(Näslund 1985). The screening program was introduced in the mid 1960s, and a reduction in the incidence of cervical cancer followed. The age standardized incidence of cervical cancer in Sweden went from 20.6 per 100000 women in the interval 1959-1963 to 10.1 in 1989-1993. (Dillner 2000). In recent years however this decline in incidence has started to level off and seems to be stable at an average of 10 cases per 100 000 women and year, see figure 1. This is not unique for Sweden but can be seen in most developed countries which have a history of cytological screening. (Mayrand 2007).

Figure 1 Incidence of Cervical Cancer in Sweden 1961-1996 Taken from "Cancer i siffor" Socialstyrelsen

About Cervical Cancer

For cervical cancer to occur, a woman has to be infected by *Human Papillomavirus (HPV).* (Bosch et al. 2002*)* There are a multitude of different strands of HPV which could be

further divided into low- and high-risk groups when looking at the risk of developing cervical cancer.

If a woman is infected with any of the high risk types of HPV she stands an increased risk of developing abnormal cell changes that could lead to cancer in the cervix. Two strands, 16 and 18, can be found in a majority of cervical cancer cases (Schiffman 2007), as can be seen in figure 2.

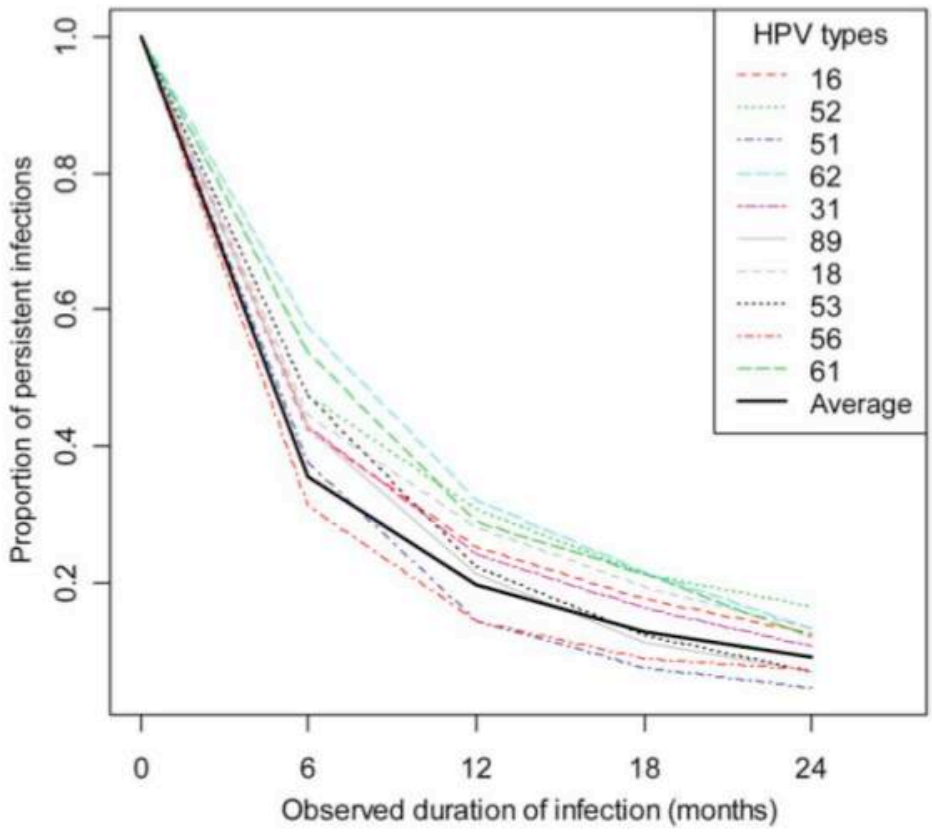


Figure 2 The persistence of HPV infections. Taken from Plummer et al 2007

The transient character of HPV

Most HPV infections are said to be transient in character, meaning that there is a high probability for a woman regressing to a healthy state if infected with the virus. Recent research has shown that most infections are indeed transient, but the relationship between time and HPV status is more complex than prior knowledge has indicated.

When studying women with confirmed positive HPV status over a period of two years the main finding was that as much as 91 per cent of the infections were gone within twenty-four months. (Plummer et al. 2007) A second finding was that infections still prevalent after twenty-four months were much more likely to stay persistent when checking after another six months. A conclusion to draw from this could be that a woman identified to be infected with the same strand of HPV infection for more than two years faces a higher risk of developing cytological abnormalities and in the end cervical cancer.

As mentioned above, a woman infected with a high risk HPV-infection faces a risk of developing abnormal cell changes on the surface of her cervix. This is called *Cervical Intraepithelial Neoplasia*, or CIN, a pre stage to cervical cancer. (Richart and Barron 1969)

The CIN state can be classified into three different levels, CIN 1,2 or 3. The first state, CIN 1 is considered low risk and this state should not be treated if discovered, according to the national guidelines in Sweden. (Rylander and Rådberg 1997) The later stages, CIN 2 and 3 will from now on be addressed as CIN2/3, to simplify the analysis. These stages are considered to be a strong precursor for cervical cancer and should therefore be treated with the appropriate method, if discovered.

If a woman with CIN 2/3 is left untreated, she faces a higher risk of developing cervical cancer. A majority of women do however still regress back to a healthy state without treatment, even when they have reached this phase. (Östör 1993)

The probability of a woman developing cervical cancer is dependent how long she goes untreated with CIN2/3. Since a persistent HVP-infection is needed for this to happen, a reasonable conclusion would be that the incidence of cervical cancer should differ with age, since the age specific distribution of HPV infections is highly skewed to women in their 20s. Figure 3 confirms this hypothesis. This is consistent with the fact that the mortality in cervical cancer is much higher among older women. (Cancer I siffror 2005,

Socialstyrelsen)

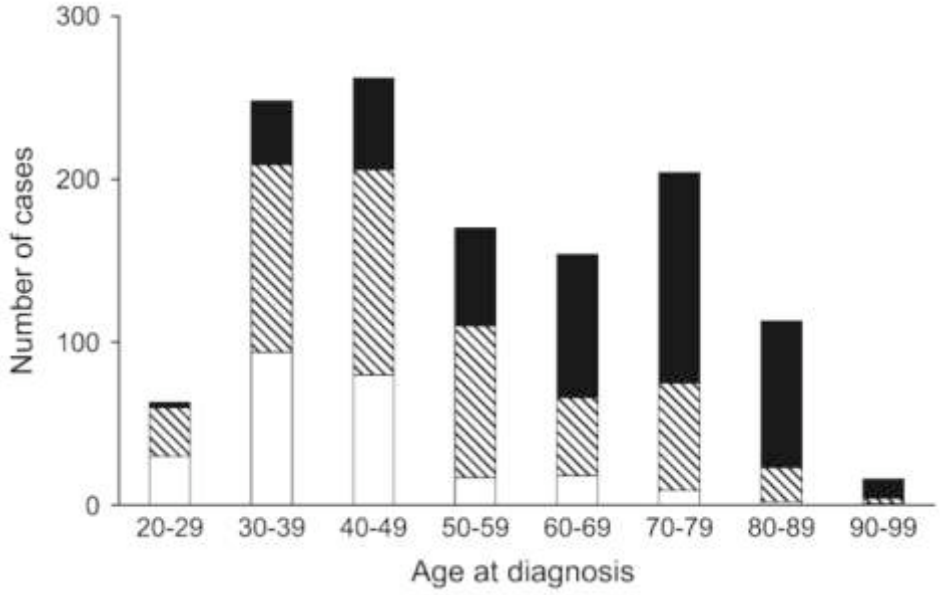


Figure 3 The bars show the age specific distribution of incidence of cervical cancer between January 1999 and December 2001 in Sweden. One can also see from the coloring of the bars how the distribution of different stages of cervical cancer differ when comparing age groups.(White is microinvasive, hatched is localized cancer and black is advanced cancer.) (Andrae et al 2008)

The Process

A complete process for a woman going from a healthy state to a state where she has a cervical cancer could be visualized as in figure 4. Notice that when she reaches any of the cancer states, she is no longer able to regress to a normal healthy state on her own.

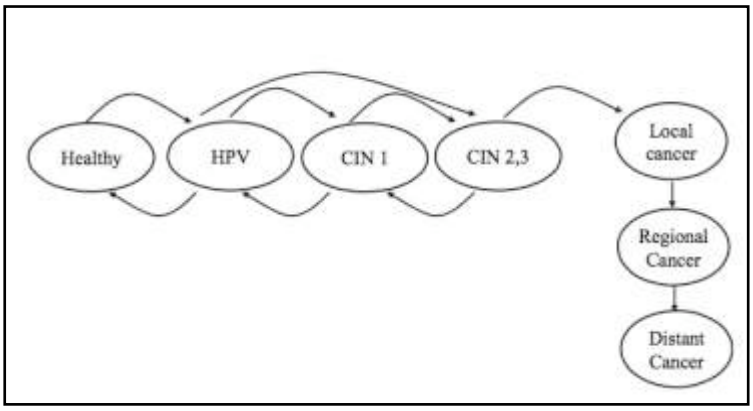


Figure 4 The epidemiological development of cervical cancer. Adapted from Kim et al (2005)

Cervix cancer is one of the most preventable forms of cancer. (Ponten et al. 1995) There are also good prerequisites for a patient to be cured early in the disease's course. (Näslund 1985)[·] However, if the cancer is untreated and reaches either a regional or advanced phase, the probability of being cured is smaller.(Interview, Strander 2008) Therefore an important parameter in the process of lowering the incidence and mortality of cervical cancer could be to improve the screening program's sensitivity in detecting women with increased probability of developing cervical cancer, in effect women with CIN2/3.

2.2 Screening Strategies

2.2.1 Current practice of Screening for Cytology

The organized screening program in Sweden is implemented through scheduled visits to a midwife every third year for all women in the age range 23 to 50. Thereafter the interval becomes every fifth year until the women reach the age of 60 when the screening stops. If a woman has reached the age of 60 and has not shown any cell abnormalities during screening period, then there is very low risk that she could be infected with HPV and develop the disease.

When a woman is called to screening, she is met by a midwife for taking a P*apanicolau smear (Pap smear.)* The midwife collects a sample of the cells from the outer opening of the cervix and put it on a slide. The smear is further analyzed in laboratory by specialized cytoscreeners that conduct analysis on the basis of a specific Pap-classification.

Sensitivity and specificity

When trying to evaluate the merits of any diagnostic test, whether in medicine or any other application, the main interest lies in how accurate and specific the test is. In statistics inference testing, the terminology talks about type 1 and 2 fault error, which are measures for how reliable the specific test is for falsely accepting or rejecting a false or true null hypothesis. In medicine, these distinctions in test characteristics are called *sensitivity* and *specificity*. The sensitivity of a test is the complement to its type 1 error rate,

or the probability of accurately detecting a positive state. The specificity of a test is the complement of the probability to falsely detect a positive state. There is often a trade-off between these two characteristics in practice; a test with a higher sensitivity implies a lower sensitivity and vice versa.

When applied to the cervical screening program, any changes to the screening practice that would lead to changes in sensitivity or specificity would lead to higher costs, although different in character. For example, if the sensitivity of the screening increases, this would imply higher short term treatment costs since more people are found to be at risk and accordingly treated. However, in the long term perspective cancer treatment costs are likely to be reduced. Note that the net cost effect could be worsened by a probable lowering of the specificity of the screening, which implies overtreatment due to false positives.

There is no consensus on the exact sensitivity of a conventional Pap smear test. Several values have been proposed with high variation. As for specificity, it could be defined as the proportion of *true negative,* or the accuracy grade that let practitioners detect truly healthy patients.

The current screening practice with the Pap smear technique only looks for the late stage symptoms of a permanent infection, CIN2/3. Earlier stages of the disease, in particular the detection of persistent high risk HPV infections, are impossible to detect with an ordinary Pap smear sample. The causal relationship between persistent HPV infection and the development of cervical cancer has been established without a doubt. (Bosch et al. 2002) However, there is still controversy as to what extent the information of a woman's HPV status can be used within a screening program. Proponents of including tests for HPV status suggest that the higher sensitivity of HPV-DNA tests could lead to an increased detection of women at risk of developing cervical cancer, and therefore lead to higher effect in terms of life years gained. (Bistoletti et al 2005) However, critics point to the fact that the prevalence of HPV is so high within certain age categories that including this factor in the screening process would lead to a lowered specificity of the screening due to false positive categories of women at risk, due to the transient character of HPV infections. The relationship between HPV prevalence, cervical cancer incidence is defined as the number of cases per 10^5 women and age as can be seen from figure 5.

Note that this figure originates from a Dutch setting but can still be informative from a Swedish perspective. This critique has lead to that most proposals of HPV categorizations in the organized screening program are targeted for women older than 30 when the prevalence of infections has decreased. (Bistoletti et al 2005)

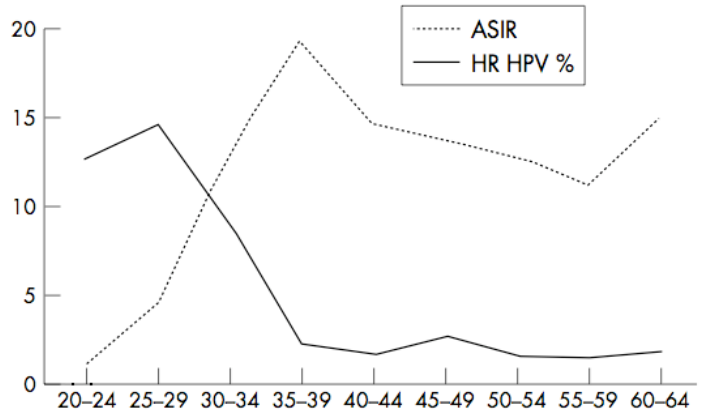


Figure 5 A comparison of the prevalence of HPV, HR HPV, and the age specific incidence of cervical cancer per 10^5 women, ASIR, from Holland. (Bosch et al 2002)

2.2.2 Treatment

Colposcopy and Biopsy

Using Pap smear tests will help pathologists to report if there are any cytological abnormalities. If the diagnosis of the cytology is categorized as a CIN2/3 the diagnosis should be confirmed by a colposcopy, an ocular inspection performed by a trained gynecologist. Just like conventional cytological screening, the accuracy of the colposcopy is estimated in terms of sensitivity and specificity. These parameters are dependent on the specific size and histological grade of the lesion. (Strander 2008) The following rationale behind this correlation is the larger the lesion, the higher the grade of CIN. This means that depending on the diagnosis of CIN2 or CIN3, the sensitivity of colposcopy differs.

From the largest study in a Swedish context up to this date, a sensitivity of 94% for CIN 3 and 83% for CIN 2 was estimated, and could therefore be applied to colposcopic investigation in our model. (Elfgren et al. 1996). Missing 100 % specificity, the

colposcopy is usually followed by cervical biopsy, which is collecting a sample of the tissue. The more extended form of biopsy is cone biopsy or conization.

Conization

After the confirmation of the diagnosis by applying colposcopy and biopsy, women with confirmed cytological abnormalities of CIN2/3 will be treated. Conization is a small surgery where a cone of the cervix is removed.

Although conization is a widely accepted treatment with a high degree of success, the cure rate is not perfect. In Sweden up to 6.5% of women treated for CIN2/3 need to have a retreatment within one year and 7.8% within two years.(Strander 2008) Still, it is difficult to say if the need for repeated treatment of these patients depends on the eventual incompleteness of the first conization or the increased inclination of this high-risk group to develop cervical cancer in the future. (Strander et al 2007)

2.2.3 New Strategies

Liquid Based Cytology (LBC)

A new cytological sampling technique called Liquid based cytology (LBC) has several new capabilities compared to ordinary Pap smear cytology. For instance, it has been suggested that due to lab technical differences between the two methods more homogeneous samples could be attained with the LBC method. This would lead to higher efficiency in the interpretation of the results and to possible cost reductions in terms of lab capacity since the LBC samples are less time consuming to analyze.

As for the sensitivity of cytology with the LBC method there is no consensus yet on the exact value, although most studies suggest that LBC has higher sensitivity than conventional cytology. (Strander et al. 2007) Regarding the specificity of LBC, the findings are more ambiguous although there is a suspicion that LBC would lower the specificity of the screening process.

The LBC technique could eventually lead to long term cost savings in terms of reduced needs of analyzing staff. This is due to the possibility of automating the lion part of the analysis. (Davey et al. 2007)

HPV-DNA Test

A recently discovered fact is that a permanent infection of HPV-virus in a patient is a very good *precursor* for the risk of developing cervical cancer. (Ronco et al. 2006) Therefore, the application of HPV-DNA testing within the screening program could be a possible improvement toward the detection and treatment of CIN 2 or 3. (Ronco et al 2006, Mayrand et al 2007, Naucler et al 2007)

The LBC method introduced above facilitates a combination of cytology screening and HPV-testing, using the same test sample for both tests. This is sometimes referred to a triage methodology.

Several countries, including United Kingdom and Canada, have already changed their screening programs by adopting these new methods.

The longevity of a true negative HPV result compared to a true negative cytology

When discussing different screening alternatives concerning the progression of cervical cancer one needs to be aware of the difference between cytological information and information about an eventual HPV infection. Since a progression of cell changes is fairly heterogeneous between patients, the interval between screening occasions needs to be short even when a true negative result has occurred. (Näslund 1985)

As touched upon previously, there are over a hundred different strands of HPV. Only around fifteen of these are believed to be a precursor for cervical cancer. Of these strands, strand 16 and 18 stand out as the most prevalent in women developing CIN2/3 or cervical cancer. Therefore the specificity of a HPV test as a screening method for detecting women at risk of developing CIN2/3 depend of how many strands one looks for in the test. Including more strands leads to higher sensitivity but also lowers the

specificity of the test. This would have consequences on the cost effectiveness of this method. (Forslund et al. 2002)

In order to create understanding of the problem addressed in this thesis, we will now move on to the theoretical and methodological aspects of economic evaluation of health care intervention.

3 Theory and methods of economic evaluation

The task of evaluating health care from a health economic perspective is always complex. Unlike a standard investment decision in a profit maximizing enterprise, it is unclear whose profit, or benefit, one should maximize. To make matters even worse, there could be conflicting objectives depending on the perspective the decision maker chooses when trying to answer the question of which intervention, if any, to implement.

From a private perspective the dominant strategy is the one that maximizes profit. A Health Maintenance Organization (HMO), a vertically integrated health care producer funded by private insurance fees, is usually privately owned. Therefore it wishes to identify health care interventions that lower the total expenditure when treating their patients. If there are several health care options that measure up to this narrow analysis, the HMO seeks to find the alternative with the highest net benefit to the their profit.

From a societal perspective, when health care production is financed by the society as a whole, which is the case in Sweden, the primary objective should be to get as much positive health improvement or maintenance as possible for a finite set of devoted resources to this cause. This means that when studying a specific treatment or a set of possible mutually exclusive treatments the resources are being spent in a manner that is efficient and fair. However, this thesis will show that this task could be sufficiently complex.

Regarding the decision considering health care alternatives that have a large and obvious positive net contribution to society as a whole; the answer is more straightforward. A decision maker should always choose to invest in an alternative that gives more resources back than it costs to implement, given that no other alternative exists that has an even higher net contribution.

In order to create an understanding of the different approaches to health economic problem solving, three different methods will now be discussed.

3.1 Different types of economic evaluation of health care

When describing the methodological issues concerning health economic evaluation it is useful to use an example. We assume two different treatments, treatment A and B, for a specific medical condition. Treatment A is the treatment currently used in the medical practice for the specific condition. However the new drug, treatment B, has been proved through several medical efficacy studies to have at least 50 per cent higher effect than treatment A for this condition. The pharmaceutical company, which conducted the research and development needed to discover this new and improved treatment, has to ask for a higher price, actually double the amount than for the current treatment A, to account for the R&D costs. How could the decision maker, in this case someone who's main interest is the utility of the society as a whole, find out if the new drug is worth the increased investment?

There are primarily three methods currently used in health economic evaluations like the current example: *Cost Benefit, Cost Effectiveness, and Cost Utility Analysis.*

3.1.1 Cost-Benefit Analysis

Cost-Benefit analysis (CBA) is an economic evaluation method that measures health outcomes in monetary terms. When a new health care programme is evaluated under CBA conditions, the relevant question is whether the incremental health improvements, recalculated into monetary values, overweigh the costs or not. If that is the case the programme is said to give *a positive net social benefit* to the society. If V_B is the incremental monetary benefit of introducing treatment B and C_B is the corresponding incremental monetary costs, the equation becomes:

$$Net\ Social\ Benefit = \mathrm{V_B} - \mathrm{C_B}$$

Health outcomes could be revalued in monetary terms with three different approaches: human capital, revealed preferences and contingent valuation, all with their respective pros and cons. The estimation in terms of *willingness-to-pay* (WTP) as a basic parameter in contingent valuation and the most common way to value health gains for participants.(Drummond et al 2005)

3.1.2 Cost Effectiveness

Cost-effectiveness analysis (CEA) is an economic evaluation method that is applied when decision-makers have to choose between different interventions within limits of a given budget or spending per output. In CEA alternative strategies are listed in order of increasing effects and then compared by using *incremental cost-effectiveness ratios (ICER).*

The ICER is defined as the marginal cost of the more expensive strategy, strategy B, divided by its marginal effect.(Kobelt 2002)

$$ICER = \frac{C_B - C_A}{E_B - E_A}$$

In the context of CEA the notion of dominance is often used. One strategy is said to dominate another strategy if it has both higher effectiveness and lower costs.(Drummond et al 2005)

In case the incremental cost-effectiveness ratio for one strategy is higher than that of the next more effective strategy one talks about extended dominance. (Weinstein 1990) In cost-effectiveness analysis the choice of effectiveness measure could depend on an objective of a specific intervention. The most frequently used measure of health effects is life years saved, or change in life expectancy. If an intermediate endpoint has been chosen as effect output, a link with the final outcome, life years saved, should be established to improve the comparability with other CEA. (Gold et al. 1996)

3.1.3 Cost-Utility Analysis

Cost-Utility analysis (CUA) is often viewed as a more advanced version of cost-effectiveness analysis in terms of its use of valued health outcomes. It has been developed as a response to existing limitations in cost-effectiveness analysis, such as its inability to properly value interventions aimed at improvement of a patient's quality of life, not just the length of life.

In CUA health outcome is measured as quality-adjusted life years (QALYs). It is used in the analysis instead of life years gained, as the denominator in the ratio cost/QALY. The

rationale behind an effective allocation of healthcare resources is the same as when looking at ordinary ICERs in CEA.

The estimation of QALYs is made by using a weight between 0 (death or well-being graded as equal to being dead) and 1(full health) for every life-year. Including quality aspects in the output measure has its benefits and drawbacks. It allows for comparison between different health economic evaluations when the same output is used (QALY). Furthermore, if the quality aspect is included in the analysis, this will allow for discrimination between alternatives that only differ in perceived quality for the patient.

When choosing the effect measure in health economic evaluation, QALYs are the de facto standard. If we would have had access to quality of life data among women with the various diagnoses in the development of cervical cancer, QALYs would have been used in the analysis. However, life years gained will instead have to suffice. Hence, our approach can be described as a cost effectiveness analysis. This will have two effects on the results of the analysis. First, gains in terms of reduced morbidity will not be taken into account. This will underestimate the effect of cervical cancer screening. Second, every life year gained will be valued as one. This will overestimate the effect of screening.(Johannesson 1996) However, these two effects level out each other to a large extent and will not be discussed further in this thesis.

Although a cost utility analysis is preferable for comparability reasons, this thesis will conduct a cost effectiveness analysis with life years gained as effect outcome in the comparison of the different strategies.

3.2 Decision rules

This part is based, if not stated otherwise in the text, completely on Karlsson & Johannesson (1996).

When conducting a cost effectiveness analysis, one needs to have a way of ranking the various treatments within a specific patient group. If several treatments exist for a specific medical condition, these should be sorted starting with the lowest effect and

thereafter adding treatments with regard to additional effect. Incremental effects and costs are thereafter calculated and ICERs are created.

There are two ways a treatment could be dominated by other mutually exclusive treatments. First, treatments which have a higher cost and lower effect than an alternative treatment are said to be dominated, see the dark grey area of figure 6. Treatments which are dominated will never be cost effective since another treatment exists with both lower costs and higher effect.

A treatment could also be said to be dominated when it has a higher ICER than a treatment with a higher effect. In these cases the dominance is referred to as extended dominance. The intuition is not as straightforward as with standard dominance. The main rational is that a decision maker can create more effect by using a more efficient treatment alternative. This can be seen in a cost effectiveness diagram where two treatment alternatives can be connected linearly, and thereby excluding one alternative in between.

The dominated treatments are thereafter sorted out from further analysis, and the ranking process and calculation of respective ICER is repeated again.

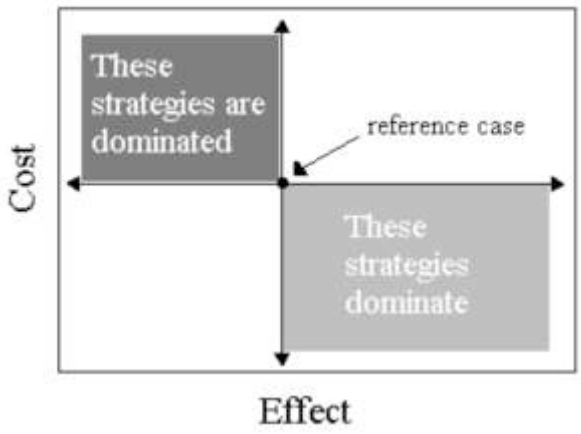


Figure 6 The Cost Effectiveness Plane.

Finally, the decision concerning which of these non-dominated treatments to choose can be made with two different techniques: the budget rule approach and the price per effectiveness unit approach.

The Budget Rule Approach

With a fixed budget approach, the real decision problem becomes how to maximize the produced health effect for a given budget. Therefore, one needs to rank all health care intervention alternatives from the base case of doing nothing and follow through with the intervention with the lowest ICER. (Drummond et al. 2005) When the expenditure considerations for all the patients in need of this specific treatment have been taken into account and if the budget is not yet depleted, the treatment with the second lowest ICER is added. This goes on until the fixed budget is depleted. There are several caveats with this method. First, one needs make the budget fictive if a societal approach is chosen in the analysis. Otherwise, costs outside the fixed budget would not be taken into account. A much larger problem is due to the lack of perfect information. For the budget rule to be consistent, for any new intervention under cost effectiveness consideration, one needs to have information about the ICER for every other treatment currently used. Note that this information problem goes outside the specific medical condition studied. (Johannesson and Meltzer 1998) Finally, there are some equity issues following this technique. One can imagine of a situation where the fixed budget is sufficient to subsidize a new, more efficient treatment considered to be cost effective, but only for a subgroup of the patient group. The residual group will have to wait until the designated budget is increased. This raises some equity issues. (Karlsson and Johannesson 1996)

The Price per Effectiveness Unit Approach

Another way of deciding which of the mutually exclusive treatments that are cost effective is through the price per effectiveness approach. A threshold ICER is calculated which acts as a ceiling for which interventions to supply. This means that the treatment with the highest ICER within a specific patient group should be chosen, given that it is below or at this threshold.

These two rules have a close relationship. A threshold ICER leads to a specific realized budget, whereas a budget rule leads to a realized threshold ICER. The threshold rule is however recommended due to practical considerations concerning both the information

problem mentioned above and the problem with establishing a fictive budget. (Johannesson and Meltzer 1998)

There are several ways one can calculate the threshold value for the ICER. Depending on the measurement unit for effect, different values can be made. Since this thesis uses discounted life years, the incremental cost per gained life year will be used as threshold.

Since the analysis is made from a societal perspective, the society's willingness to pay (WTP) per life year gained (LY) is the relevant value to estimate. One way to do this is to find the value of a statistical life from other assessments. The WTP/LY can be derived from this number by dividing this number with the average number of years gained by the saving of the life. We use the estimated value for a statistical life from the Swedish Road Administration. Their latest figures are from 2005 and are therefore adjusted for two years of inflation. The value for a statistical life is approximated to be 17.079 million sek. This value is already increased with a factor of 1.53 to account for welfare losses due to excess burden of taxation for the financing of roads and general value added tax in Sweden. Cost effectiveness calculations do not take these effects into consideration and this factor needs to be eliminated from the estimate for consistency reasons. (Johannesson and Meltzer 1998) The average discounted life years lost in a traffic accident are 19.6 years, using three per cent discount rate. The WTP/LY estimate is therefore approximately 593000 sek. The calculation is as follows:

$$\frac{WTP}{LY} = \frac{17079000\ sek}{19.6 * 1.53} \approx 593000\ sek$$

This value will therefore be used as the threshold when deciding which screening strategy to be cost effective.

3.3 Measurements and definitions of costs and effects

As touched upon previously, several perspectives can be adopted when conducting a cost effectiveness analysis. This has direct implications for the measurements and definitions of different costs and effects. The narrow scope of the private health care producer is not sufficient from a societal point of view. For instance, the net savings associated with

the impact a specific treatment has on a patient's long run productivity should, when possible to quantify, be included in the analysis. (LFNAR 2003:2)

This thesis focuses on different alternatives to minimize the prevalence of cervical cancer through organized screening. In Sweden this screening is publicly funded through the county councils directly and indirectly through the tax payers. Therefore the most suitable level of analysis to adopt when evaluating the cost effectiveness is through a societal perspective with the broadest definition of costs and effects.

3.3.1 Costing

If a societal perspective is chosen in the cost-effectiveness analysis then it is appropriate to initiate such costs as intervention, morbidity and mortality costs. The listed costs are further divided into direct and indirect costs. This is the classic approach and has as such also been our choice of cost definition. We have chosen to focus on the direct and indirect costs associated with the intervention. However, morbidity and mortality costs are preferably also included in health economic evaluation. (Drummond et al. 2005) Due to a lack of data on these latter aspects, we have not been able to fully address and asses these costs in the analysis. This will underestimate the cost effectiveness of the screening.

Intervention costs

Direct medical costs of the intervention refer to health care costs related to the diagnosis, the treatment and the follow-up. Health care could be provided either in inpatient or outpatient settings. In inpatient settings, where the patient is treated in a hospital, costs could be calculated by adopting either the *per diem method* (bed price/day* n days) or the *DRG method* based on diagnosis and age. In outpatient settings, costs for physician visits, midwife visits, diagnostic tests and procedures are central components.

Examples of indirect costs relating to the intervention could be travelling expenses and time costs accrued to patients in association with the treatment. In order to get access to health care a patient has to bear additional personal costs.

In the context of cervical cancer direct medical costs could be presented as the screening costs including invitation, midwife or physician visit, laboratory analysis costs and follow-up costs. Furthermore, the detection of the precancerous stages will take place in the outpatient setting. If we deal with later stages of cervical cancer prevention and treatment, these are provided in the inpatient settings, i.e. a hospital.

As for indirect costs of the screening, the time cost for the woman participating in the screening would be relevant to include in the analysis, using national average hourly earnings as an estimated proxy for this value.

Morbidity costs

If production changes of morbidity should be included or not is somewhat controversial issue in health economic evaluations and several arguments against this practice have been suggested. One argument is that when using QALYs in the cost effectiveness analysis there is a risk that costs related to the morbidity effects of a disease is already taken into account with the quality weight of the disease. There is a risk of double-counting this effect. A counterargument would be that individuals do not bear the full costs of changes in their productivity relating to increased morbidity. In countries as Sweden with generous sick leave benefits, this effect is even more accentuated.(Siegel et al. 1996) Another argument against the inclusion of morbidity costs is the idea of the friction cost method, which suggests zero transaction costs and perfect substitution conditions for replacing labor input, due to reasons such as the constant existence of unemployed people. Due to imperfections in the labor market(Koopmanschap et al 2005) this argument has been proved to be inconsistent from a societal perspective.(Johannesson and Meltzer 1998) Thus, the inclusion of production changes in morbidity costs would provide decision-makers with more relevant information regarding which medical interventions to prioritize.

Furthermore, for an assessment of morbidity costs it would be reasonable to make a distinction between direct and indirect costs. Increased health care costs could be divided into the costs in the first year followed by the annual costs in subsequent years. For the

measurement of productivity losses one can use the forgone income related to the treatment.

Our analysis includes a crude measure of the morbidity cost relating to the lost market production attributable to the medical intervention of cervical cancer. The focus is primarily put on lost production associated with the treatment of different cancerous stages. Due to lack of data, an assumed average sick leave of one month for the treatment of cervical cancer is included, but only in the sensitivity analysis. Note that there are morbidity costs related not only to the treatment of cervical cancer but also to the condition itself. These costs are excluded due to lack of data but should be included for consistency reason. Otherwise, a risk of underestimating the cost effectiveness is present.

Mortality costs

Mortality costs could either contribute positively or negatively to the cost effectiveness of a specific treatment, when adopting a societal point of view. These costs relate to the direct costs of increased consumption of future health care due to added life years. The indirect costs are the present value of the net of an individual's current and future production and consumption in added life years for a specific medical intervention. (Meltzer 1997) For interventions specifically targeting a younger sub group of the population, the indirect cost usually increases the cost effectiveness or decreases the ICER, due to the fact that people that are still working usually produce more than they currently consume. For older subgroups both costs tend to decrease the cost effectiveness or increase the ICER for a specific treatment, since older subgroups have a higher foreseeable consumption of health care inputs and consume more than they currently produce. (Johannesson et al. 1997)

Cervical cancer is by nature a life-threatening disease and the outcome is binary: either the patient is cured through treatment or she will eventually die. Screening is applied to detect precancerous stages and identify patients where relevant medical treatment could lead to a full recovery, in other words, to an increase of the life expectancy of the patient. Since the screening has clearly been proven to lower the incidence and mortality of

cervical cancer, the proportion of elderly women in the population will thereby increase. The additional health care treatment demand that aging entails is therefore a relevant indirect mortality cost from the screening. However, the screening is targeted at women aged 23 to 60, a subgroup where most people are still working and thereby have a positive net regarding their individual production and consumption. Therefore one could argue that the direct and indirect costs of changes in mortality due to cytological screening work in separate directions and could eliminate each other. This effect and the limited scope of this thesis lead to the exclusion of morbidity costs in the cost effectiveness analysis.

We have chosen to focus on the direct and indirect costs associated with the intervention. However, morbidity and mortality costs are preferably also included in health economic evaluation.(Johannesson & Meltzer, 1998) Due to a lack of data on these latter aspects, we have not been able to fully address and asses these costs in the analysis. This will underestimate the cost effectiveness of the screening.

3.3.2 Effectiveness

In a cost effectiveness study, estimating the effectiveness is the second major task at hand. Life years gained (LY) will be used as the health effect output, due to reasons previously addressed. The appropriateness of using life years gained as an estimate for effect of the treatment could be questioned as it neglects how the disease affects the health state and consequently the quality of life for the individual. However, as previously argued, the binary nature of the outcome of cervical cancer treatment should remedy this limitation.

3.3.3 Discounting

Discounting of costs related to a specific treatment is fairly straightforward. The method we apply is a traditional present value calculation which could be found in any finance textbook:

$$P_0 = \sum_{n=0}^{t} C_n (1 + r)^n$$

Discounting of effects is not as straightforward as discounting costs. Depending on which perspective one chooses to adopt, different alternatives are possible. Some argue that costs and effects in a cost effectiveness analysis of a specific treatment should be discounted differently. The argument put forth is that individuals may discount their personal health differently compared to other monetary items, rendering market data on real interest rates on different investment vehicles useless as a proxy for their time preference of health. Discounting health improvements makes future generations' health benefits of a current treatment less valuable. Some argue that this would lead to a bias towards the present generation which could be avoided with differentiated discount rates for costs and effects. (Drummond et al. 2005)

Either one can choose to make the calculation using nominal input values and using a nominal interest rate, or one can choose real values and real interest rates. For the sake of consistency we will use the same discount rate for costs and effects with 3 per cent as the base value. This is the standard that the Swedish Pharmaceutical Benefits Board recommends. In the sensitivity analysis a range covering 0-5% will be used.

In order to provide a contextual understanding of the topics discussed in this thesis, we will prior to our analysis first briefly present the recent research in the field.

4 Recent Studies

4.1 Economic Evaluation Studies

The last couple of decades have brought about a broad range of insights concerning the essential parameters in evaluating the cost effectiveness of cervical cancer screening programmes. Screening frequency, differences in disease prevalence in the underlying population and finally alternative diagnostic techniques have all been identified as relevant topics to study. In recent studies screening frequency, age stratification and alternative screening strategies have been brought into focus.

Goldie et al. (2004) have presented qualitative insights into cost-effectiveness analysis of HPV-DNA testing and studied different alternative screening strategies using annual cervical cancer screening with conventional cytological test (Pap smear) as a benchmark in comparison with other conceivable strategies. The most cost effective alternative has proved to become 2 or 3 year interval screening with either LBC with HPV-DNA testing for equivocal results or HPV-DNA testing in combination with cytological test for women at age of 30 or more. (Goldie et al 2004)

Interval frequency and incorporation of HPV-DNA testing have been targeted issues in the study presented by Bistoletti et al. (2007) who actually initiated a Swedish cost-effectiveness investigation applied for cervical cancer screening. By considering various strategies, in particular no screening, convent ional screening, triennial screening in combination with HPV-DNA testing and combined cytology with HPV-DNA testing with 9 years' interval, the last one was stressed and proved to be the lowest cost alternative as it somewhat increased life expectancy and improved negative prediction value. Taking into consideration a progressive nature of cancer with 10-15 years *latent period*, 9 years' screening interval has been viewed as a reasonable response to cervical cancer debate. (Bistoletti et al 2007) The study presented by Bistoletti et al is used in our thesis as a reference with regard to its relevance and actuality. Moreover, we find this study relevant as it describes the screening practice in Sweden and comprises up to date data.

Another application of Markov model in the context of cervix cancer could be found in the study presented by Siebert et al. (2006). Operating in the German health care context, Siebert et al developed a decision-analytic Markov model for the natural history of cervical cancer and screening evaluation. By examining screening strategies in particular no screening, annual Pap smear and Pap smear every 2,3 and 5 years, it was shown that extending the screening interval from 1 year to 2,3, or 5 years lead to higher screening effectiveness. This study is less relevant for our analysis although it still provides some valuable insights.

4.2 Medical Efficacy Studies

Previous studies on medical efficacy have covered a broad spectrum of different alternative screening strategies. Since the cytological screening is the oldest and most commonly applied practice detecting practice across countries, it has been often taken as a base line and compared to other detecting techniques.

Paraskevaidis el at. (2004) have performed a comparative analysis of the previous investigations. The conclusion is that despite the revealed heterogeneity in the design, the population, the intervention and the follow-up practices across various studies, the relatively new method HPV-DNA testing has proven to be more effective than cytological screening. As it has better sensitivity it is recommended to be used as a complement to conventional cytological screening.

In line with the stated, Arbyn et al. (2006) underline the importance of adding HPV-DNA testing to cytology by arguing for its higher sensitivity both in absolute as in relative terms, although aware of lower specificity in deleting the absence of CIN 2/3 compared to conventional cervical cytology. (Arbyn et al 2006) Moreover, a high negative predictive value for HPV-testing has been raised by Nobbenhuis et al. (2001).

Recently a new technique liquid-based cytology (LBC) has been introduced and compared to conventional cytology. A comparison of the sensitivity of the conventional Pap smear and LBC has been presented in the meta-analysis of 14 studies. The

conclusion is that up to 12 per cent sensitivity could be improved using LBC in the detection of abnormalities of low-grade CIN. (NICE 2000)

Clinical effectiveness of the LBC method applied to the Swedish women has been examined in a recent study presented by Huddinge hospital group. Due to its higher sensitivity LBC in combination with HPV-DNA testing could be a preferable screening method to women who show minor cell abnormalities. (Andersson 2003)

With this background in mind, we will now move onto to the methodological aspects of the research conducted within this thesis

5 Method

The problem at hand is to estimate the cost effectiveness of the following three strategies:

1. The current practice with cytological screening every third or fifth year as base case.
2. The substitution of conventional cytological sampling with Liquid Based Cytology (LBC), ceteris paribus.
3. Introducing LBC combined with HPV-DNA primary screening and cytological analysis as a triage method.

The question of what strategy to implement in order to most effectively minimize the incidence of cervical cancer in Sweden, is complex. When undertaking a cost effectiveness study it is important to model the epidemiological development of the disease as correctly as possible.

The long time span involved in the development of cervical cancer, as well as the complex transitions between the many stages, renders a traditional decision tree approach insufficient to structure the model. (Drummond et al. 2005) Instead, a state transition model could be used.

A common state transition model used in health economics modeling is the markov approach. In our analysis we will use a specific version of this technique as our main analytical tool when structuring the problem at hand.

5.1 The Markov Model

The underlying assumption of a Markov model in its standardized version is independence from past events, the so called Markovian property. (Drummond et al. 2005) This means that irrespective of which state an individual in the model comes from, she will still face the same transition probabilities as someone who has another past state. This special form of a Markov model is called a markov chain model. This property is

not appropriate when modeling the epidemiological development of cervical cancer. The model needs to have a memory, or be able to remember how long a woman has had a specific condition. This is reached through a special technique that we will present further on. However, we will first present the more general outline of the model.

The markov model represents a process were the cohort of women pass through specific discrete states. From each state, these women can either progress to new states, regress to old states or stay in the same state.(Sonnenberg & Beck 1993) The probabilities for the transitions in either direction are dependent on many variables such as age, current state and the number of cycles spent in that specific state.

The model is by definition a deterministic markov model. What makes the model deterministic in comparison to a stochastic model is that the parameters put into the model are used with their expected value instead of taking into account each parameter's probability distribution and running several iterations, called Monte Carlo Simulations.

5.1.1 Model Design

Our markov model has been developed to simulate a hypothetical 23 year old cohort of women, who are followed through the screening process for each year until they reach the age of 60, the point when women in Sweden end their engagement within the organized screening, although some county councils send out invitations to women until the age of 65.

In the model, time is divided into cycles. The choice of cycle lengths could be motivated by clinically appropriate time intervals. (Sonnenberg and Beck 1993) The logic behind the choice of cycle time is to cover the events that change over time in successive cycles. In our model each cycle represents one year.

Markov States

Thirteen specific states have been defined in our model, ranging from healthy to dead, featured completely in figure 8. At the start of the modeling process patients are distributed among the various states with an initial probability. In the model it is assumed

that women initially can only be either healthy or HPV positive. This is an oversimplification since there are cases in the real world, although uncommon, where young women demonstrate advanced cellular abnormalities and even cervical cancer before the age of 23.(JHjerpe 2008) Through each successive cycle patients may either progress from the current state to a new, more advanced state, stay in the same state or regress to a partial or full recovery.

The markov states in the model are mutually exclusive; hence each patient can be in only one state at a time. As a result, some transition probabilities are time dependent and vary over the cycles, or when a woman stays more than one cycle in a specific state. One of the most obvious examples of time dependent transition probabilities is the residual mortality, the average risk of dying for any given age, which increases over time with age for the studied cohort. Another example is when a woman has an HPV-infection for several years. The transition probability to progress to a CIN2/3 state decreases first rapidly for the first two cycles and increases thereafter again. (Plummer et al. 2007)

Memory

When studying complex long term medical conditions such as the development of cervical cancer it is necessary to introduce some sort of memory. The basic version of a markov model does not include an element of memory. This means that for every cycle, the probabilities to reach any of the specific states are the same as the last cycle.

The transition probabilities which are dependent on the number of cycles spent in a specific state is a technique for creating an element of memory in the model. Another way to solve this is to introduce specific states for women who have received a treatment. This is relevant when studying cervical cancer since it has been shown that women who have received a conization for their identified CIN2/3 conditions, have a long term increased risk of developing cervical cancer, lasting perhaps as long as twenty five years after the conization.(Strander et al. 2007) Therefore a specific state for these women is introduced in the markov model to take this effect into account.

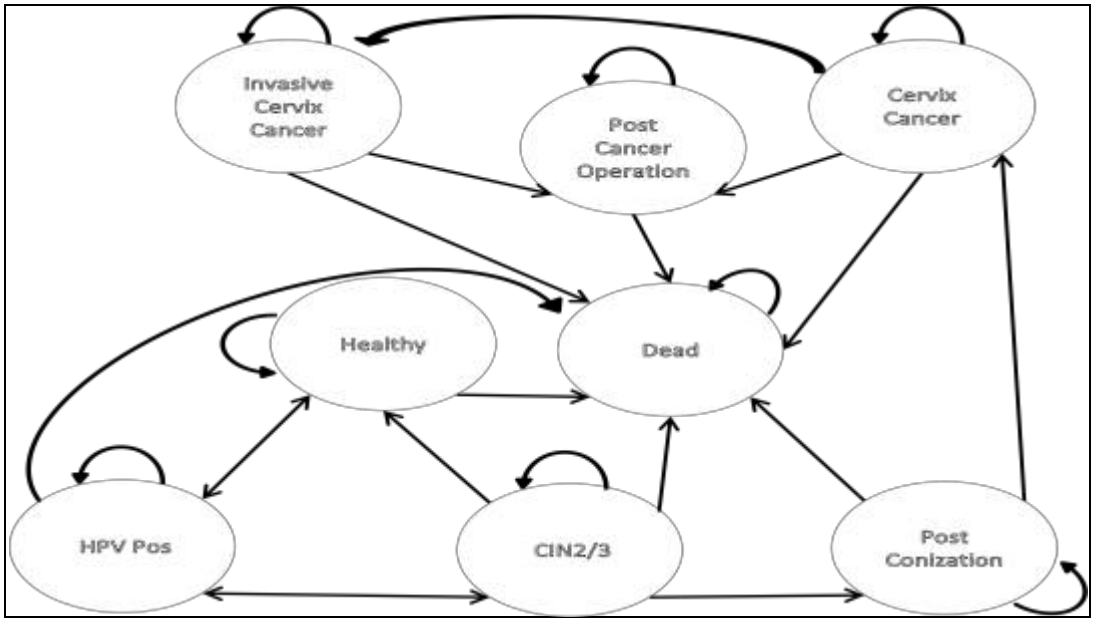


Figure 7 A bubble diagram simplified representation of the different markov states in the model. Note that some states permit that a person "self regress" to an earlier state, modeled as double headed arrows.

In the bubble diagram in figure 7 a simplified view of the markov model is presented. This illustration does not show the distinction being made in the real model between false and true markov states. The real model takes into account the possibility that an individual could be falsely designated or treated for a specific condition, since no screening or test method has a 100 per cent sensitivity or specificity. To model this we have included falsely identified states for every condition except post treatment states for cancer, although not shown in figure 7. We make the assumption that the specificity is 100 per cent for the diagnosis treatments colposcopy and biophsy. In other words, the probability of a false positive for these diagnostic methods to detect a micro invasive or larger cervical cancer is assumed to be zero. These tests are needed to be positive for a cancer operation to occur.(Strander 2008) Therefore there are no falsely post cancer treated states in the model.

The bubble diagram also does not show the various post treatment operation states that the real model includes.

5.2 Cycle Tree

One can visualize the model through a cycle tree representation, as in figure 8. It is difficult to show the complete model without using a computer monitor's capability of zooming in and out in the TreeAge software, but a simplified version is shown in figure 8. For a more detailed version of this visualization, see appendix.

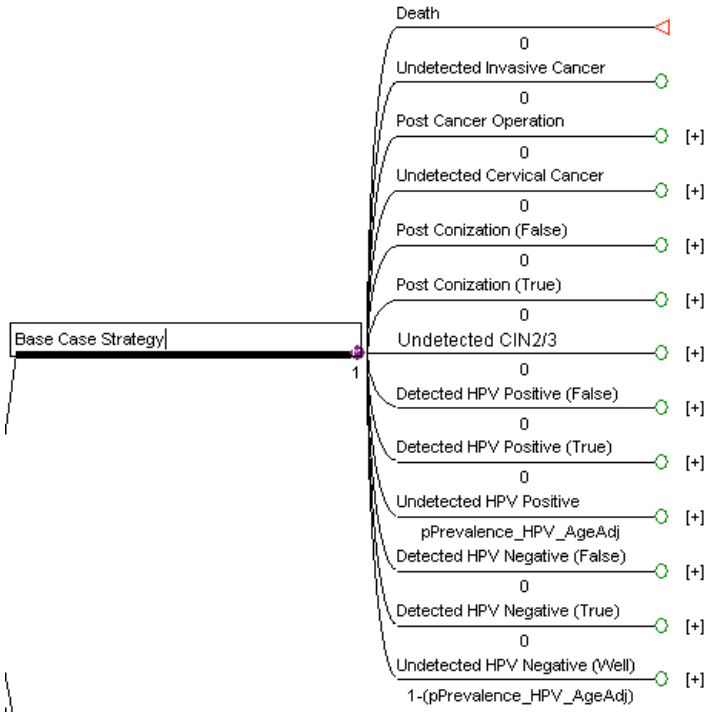


Figure 8 A cycle tree representation of the base case strategy, which is an attempt to model the current screening program. This is the first level of branches in the markov decision tree and all states except for the death states have several higher

From the cycle tree, one can see that the initial distribution of the cohort is divided between only two states, undetected HPV negative and undetected HPV positive. Both of these states are undetected by default since at the age of 23, which is the starting age of the cohort, no one has participated in the organized screening in Sweden. All other states are either attainable through the cycles or not at all, depending on the strategy under study.

In the cycle tree, which has a branch leading from the base case strategy, the cohort is not able to reach any of the HPV detected states since no HPV-DNA tests are

performed in the current screening program. When studying the strategy with primary HPV DNA testing, these detected HPV states are attainable.

5.3 Input Parameters

In our model we have created over 60 different parameters. Adding to this, at least seven tables are used for specific variables which are either age dependent or time dependent regarding how long an individual has spent in a specific state. Therefore, only a small selection of variables is presented in this section, see table 1. For a complete presentation and references, see appendix 1.

Input parameters	Value
Country Specific	
Compliance for screening	72%
Age of Screening	23-60
Screening interval*	3-5 yrs
Effect data	
Sensitivity conventional cytology	78%
Sensitivity liquid based cytology (LBC)	89%
Sensitivity HPV-DNA test	95%
Sensitivity Colposcopy/Biopsy(CIN2/3)	70%
Specificity Cytology (CIN2/3)	92%
Specificity LBC (CIN2/3)	89%
Specificity HPV DNA (High risk)	70%
Cost data	
Alternative cost patient/h	SEK 440
Physician/h	SEK 1,300
Midwife/test	SEK 80
Follow up with physician	SEK 1,740
Cytological test total	SEK 595
LBC cytological test total	SEK 639
LBC HPV primary screening total	SEK 830
LBC HPV analysis marginal cost	SEK 300
LBC Cyt analysis marginal cost	SEK 210
Biopsy and colposcopy total	SEK 5,543
Operation Conization total	SEK 8,725
Operation Cervical cancer total	SEK 14,045
Operation Invasive cancer total	SEK 124,931

Table 1 A selection of parameters used in the markov model.

It is necessary to adjust the markov model to a Swedish context. There are many model parameters affecting the screening effectiveness that differ between countries. In table 1 these are presented.

The effect data of the different screening techniques are taken from several medical efficacy studies. It is problematic to use these values, due to heterogenic conditions concerning the underlying prevalence of HPV infected or CIN2/3 affected women between different countries. However, this is the data available and as such, it must suffice.

The cost data is partly derived from a Swedish cost effectiveness study on the cervical screening program, and adjusted for two years of inflation. (Bistoletti et al, 2005) The time cost for patients are approximated through GDP/hour 2007 and added to each total treatment cost.

In table 2 the most important transition probabilities are presented. Many values are only the first table value, due to some type of time dependency. See the appendix for a complete presentation of these tables.

Transition Probabilities	Value
Time Dependent	
HPV to Well(neg related)	69.00%
Screening retest if HPV positive(<3 yrs)	100.00%
Screening retest if post conization (<4 yrs)	100%
Age dependent	
Well to HPV positive(23 year old)	39.00%
HPV to CIN2/3 (<35)	1.73%
HPV to CIN2/3 (>35)	5.95%
CIN2/3 to Well(<35)	10.27%
Residual death risk (23)	0.03%
One year probabilities	
Cervix cancer to dead	7.56%
Invasive cancer to dead	20.00%
CIN2/3 to Cervical cancer	0.15%
Cervical cancer to invasive cancer	20.15%
Post Conization to CIN2/3	10.00%
Assumed	
Screening retest for cyt2/3 confirmed	100.00%
Expected life year left well	25
Expected life years left post conization	21
Expected life year left CIN2/3	18
Expected life years left post cancer operation	15
Expected life years left cervical cancer	11
Expected life years left invasive cancer	9

Table 2 Transition probabilities used in the markov model

5.4 Model Assumptions

Screening

We assume one compliance value for all women participating in the screening program will follow the latest average from a Swedish context, although there are large differences between different county councils and also between age groups. (Dillner 2000, Gynekololgiskt kvalitetsregister 2007)

In the modeling of primary screening for HPV-DNA status, it is assumed that women who receive a positive HPV but negative reflex cytological sample have an increased compliance for future screening during the following three years.

Women treated for CIN2/3 have an increased probability of screening for the following nine years, independently of the test result. This is also the case for women treated for cervical cancer.

Under the strategy for primary HPV-DNA screening, women that are designated to be HPV negative receive no screening offer for the next six years, irrespective of age.

Epidemiological development

We assume that when treated for CIN2/3, or the post-conization status in the model, a woman has been cured both from the cell abnormalities and from the HPV persistent infection (Elfgren et al 1996), although we take into account that she has an increased risk of progressing both to a CIN2/3 state and to cervical cancer for as long 25 years.(Strander et al 2007)

Life Expectancy

Each cycle spent in any state, death excluded, will lead to an incremental effect of one year. Naturally, when a person reaches the death state, no more calculations are made. Instead the costs and years lived are summed up for that specific woman. When the model stops, after 37 cycles, the surviving women have reached 60 years of age and are given an estimate of the expected years left to live, discounted back to that time. This number is varied, depending on which stage an individual is located in when the model stops. Women located in the advanced stages such as CIN2/3, post treatment states or cancer states are given less years than women in the healthy or HPV positive states, as their conditional probability of survival is lower compared with healthy or HPV positive women. To the latter group the estimated effect has been derived by adding the expected years left to live for 60 year old women. (SCB Statisktisk årsbok 2007) For the other states, an arbitrarily difference has been chosen.

Costs

The costs associated with any given activity under either the current screening practice or the proposed alternatives, is added uniquely for each individual passing through that specific arm in the model. For instance, a woman not participating in a proposed screening opportunity does not induce any incremental related medical cost for this activity, compared to a woman who indeed does comply and participate. The cost dimensions used in the base analysis is the direct interventions costs and the time cost related to these interventions. The morbidity costs and mortality costs have been excluded due to lack of data. This will underestimate the cost effectiveness of any intervention that lowers the incidence of these events.

Uncertainty

To validate the model for uncertainty and test the robustness of the conclusions, a one-way sensitivity analysis is undertaken for the parameters that we assess to be of highest importance in the cost effectiveness analysis. Hence, some of these parameters are varied, while the other parameters are held constant. The possible range in variation has either been defined with reference data on the possible spread of a specific parameter. However, in many cases such data has been unavailable, and ranges have then been defined arbitrarily as +/- 50 per cent from their base value.

If the main conclusion still holds for these variations, one could argue that the results are less sensitive to uncertainty in the parameters. This technique to account for uncertainty has mainly three limitations: arbitrariness in the choice of variables under study, the choice of range in which to study these in and finally the risk of neglecting correlations between different variables. (O'Brien et al. 1994)

A more realistic approach could be to let the uncertainty for each specific parameter, for instance the sensitivity of cytological screening, is taken into account through a stochastic markov model. This is called a Monte Carlo Simulation and could best be described as a process where the computer throws a die for any individual simulated in the model, hence the name Monte Carlo, for each parameter going into the analysis. The process is repeated many times, often in the numbers of 10^4 or more. For this to be fruitful, the

creator of the model needs to either know or have some expectations about the probability distribution for each parameter simulated in the model. This method requires extensive empirical data on the parameters for any assumptions on their respective distributions to be valid. Therefore, we will not perform Monte Carlo simulation in our markov model.

5.5 Software

The building and simulation of the markov model has been created with TreeAge Data Pro 2008.TreeAge Data Pro is a specialized decision tool software, often used in cost effectiveness calculations, for example applied to health care production. The software facilitates the construction of complex decision trees and markov models through a graphical interface. The calculations regarding the cost effectiveness and the sensitivity analysis has also been undertaken with this software.

6 Results

In an initial step in checking the validity of the markov model we study the expected undiscounted value of the effect measure, in this case the expected life years of the cohort of women going into the model. The model starts when the women start their cytological screening at age 23, hence their expected life years should be congruent with the real expected life years left at that age, which is 60.2 years for 23 year old women in 2007.(SCB Statistisk årsbok 2007) Note that this figure is undiscounted life years. The model gives a value of 58.57 years for women in the base case strategy, which is an attempt to closely model the current practice of screening. Therefore, the model slightly overestimates the mortality rate of cervical cancer, since the risk of dying is categorized into two separate risks, the risk from cervical cancer and the residual risk of dying. This overestimated mortality will lead to a lower ICER for any treatment that lowers the incidence of cervical cancer, ceteris paribus. This effect should not asymmetrically favor any of the alternatives under evaluation, since they are all based on the same model design.

A representation of the difference in the effect of the three screening strategies can be seen in figure 9. Note that the difference in survival between the current cytological screening strategy and Liquid based cytology, compared with primary screening for HPV-DNA, increases as the cohort gets older. This can be expected when taking into account the age dependent mortality of cervical cancer, already visualized in figure 3 in section 2.

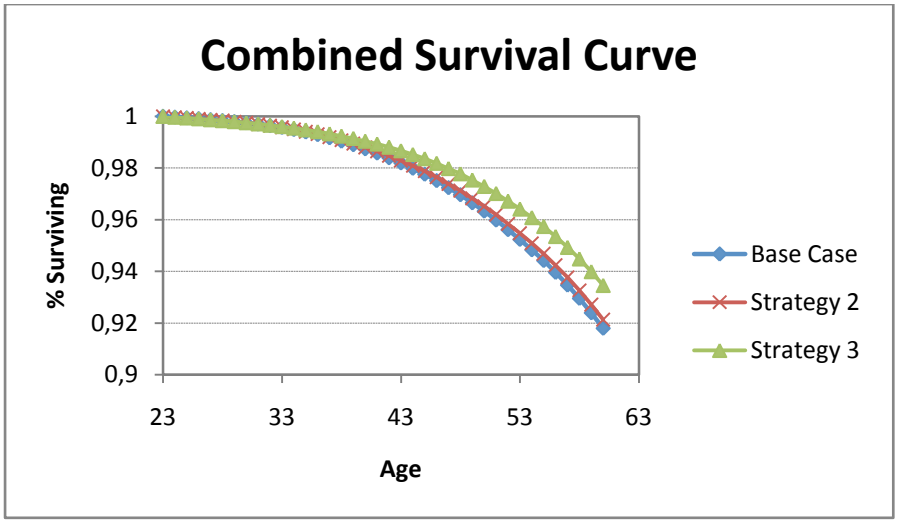


Figure 9 A survival curve diagram of the three different strategies.

6.1 Cost effectiveness

When running the cost effectiveness analysis with a discount rate of three per cent for both effect and costs, the result can be seen in figure 10. From this, we can draw the conclusion that strategy two, substituting the conventional screening methodology with liquid based cytology, is dominated by strategy three, primary screening for HPV-DNA and reflex test for cytology from the same LBC sample.

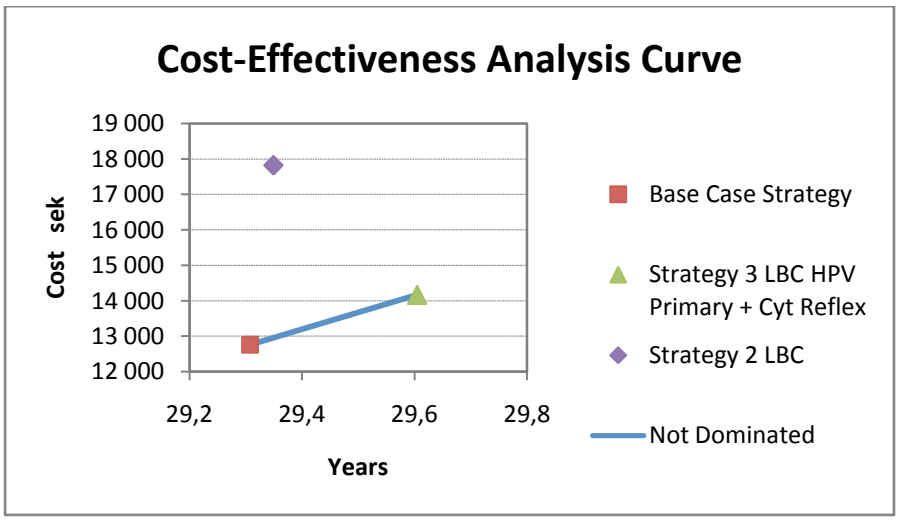


Figure 10 The Cost Effectiveness diagram. Notice that the slope between the base case strategy and strategy 3 is actually the ICER for strategy 3.

This means that strategy 3 is both more efficient, in terms of decreasing the incidence of cervical cancer, and costs less than strategy 2.

When ranking the alternatives with respect to increasing effect, table 3 is produced.

Cost Effectiveness Output	Cost	Incr Cost	Eff	Incr Eff	Incr C/E (ICER)
Base Case Strategy	12.8K skr		29.308 Yrs		
Strategy 2 LBC	17.8K skr	5.7K skr	29.349 Yrs	0.041 Yrs	ICER 139.02K
Strategy 3 HPV Primary + LBC Reflex	14.2K skr	-3.6k skr	29.605 Yrs	0.256 Yrs	ICER -14.06K

Table 3 Cost effectiveness Output for all three strategies

One can clearly see the dominance in terms of the negative value of the ICER for strategy 3. At first glance, this conclusion could appear to be counterintuitive since introducing a more expensive screening method as HPV testing for primary screening would lead to higher and not lower screening costs. However, with the introduction of HPV-DNA testing as a primary screening method, the information from the test result can prove valuable, independent of the result. If the HPV test is positive, the reflex cytological test will tell whether the woman needs to be rescheduled for a more costly visit to a gynecologist and a colposcopy and biopsy. This will increase the specificity of the screening, since both tests need to give a false positive if a unnecessary referral to further physical examination would take place. If the HPV test is negative, one can assume that the probability for that specific woman to develop cytological abnormalities the following years is relatively low and can accordingly place her in a low risk group with longer screening intervals. The cost saving here comes from fewer unnecessary referrals to more costly investigation, i.e. increased screening specificity.

The higher effect from strategy 3 is not as straightforward as the cost savings, compared with strategy 2. One reason could be the high sensitivity of HPV, relative to LBC. The information that a woman is positive for HPV will not solely lead to a treatment but could still be of value for the effect of the screening. These identified HPV positive women could be categorized as a subgroup with an increased risk of developing cellular abnormalities, and could therefore be offered shorter screening intervals. This would lead to a higher aggregated sensitivity of the screening. Another possible reason could be the model assumption that women identified to be HPV positive will have a higher propensity to comply with further investigation in the future, compared with women

who receive a negative result from a cytological test under strategy two. Both these dimensions would lead to higher sensitivity of the screening.

The higher effect of strategy 3 can also be seen when comparing the probability that the cohort is in the undetected CIN2/3 state in figure 11 and figure 12. The minimization of this probability is the whole purpose with the organized screening program.(Hjerpe 2007) Notice also the lower prevalence of people with an undetected HPV positive state in strategy three, which is expected since this strategy contains primary screening for HPV status.

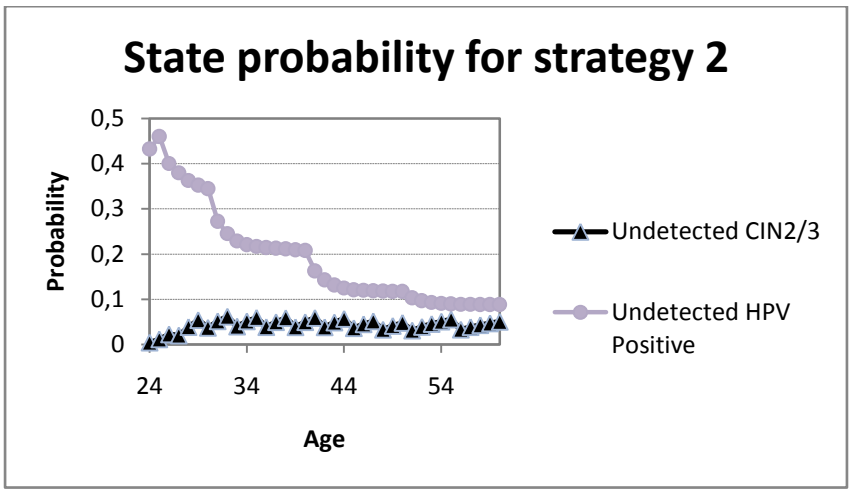


Figure 11 The prevalence of undetected HPV positive women decreases with age, as expected

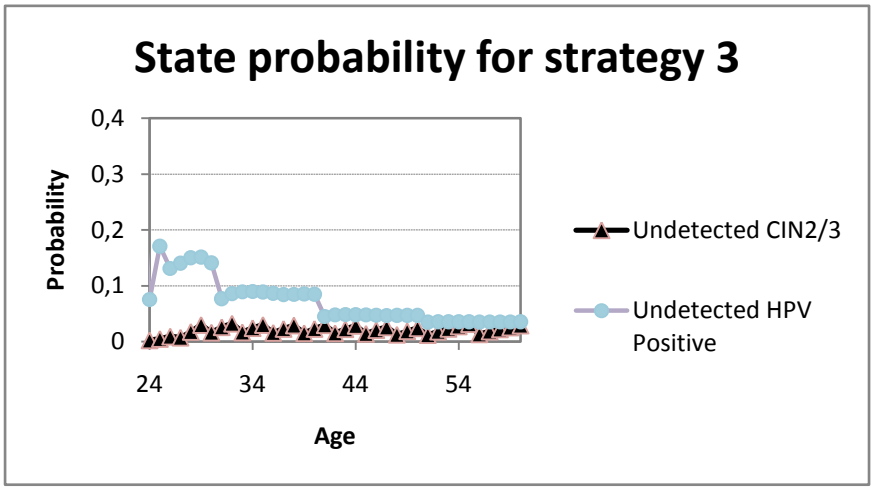


Figure 12 The prevalence of undetected HPV positive women is lower than under strategy 2 due to primary screening for HPV status

The rate of correctly detected HPV negative people is interesting from a cost perspective. In the model, these people are put in a low risk group and will receive their next screening offer after six years instead of three. This will save resources due to less demand for screening capacity. It is important that people are not falsely categorized as low risk. In figure 13, one can see that the false negative risk converges to zero as the women gets older, due to two reasons. First, the prevalence of HPV decreases with age. Second, as the women get older, they are invited to screening again, although not as frequently as if not categorized as low risk. The probability that a woman is designated with a false negative HPV test is low, due to the relatively high sensitivity of the test.

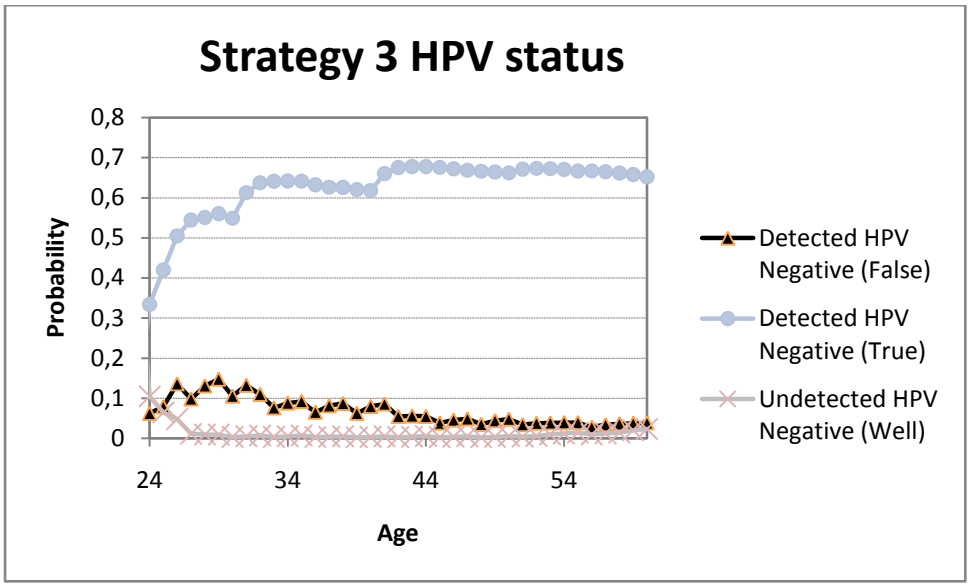


Figure 13 The falsely designated HPV positive converges to zero as the age of the cohort increases

To summarize, the primary screening for HPV in combination with a reflex test for cytology using the LBC method, clearly both saves resources and increases the detection rate of the screening program, compared with solely screen with LBC. The question remains if it is cost effective.

When excluding the dominated strategy 2 in the cost effectiveness analysis, table 4 is produced.

Excluding the dominated strategy 2	Cost	Incr Cost	Eff	Incr Eff	Incr C/E (ICER)
Base Case Strategy	12.8K skr		29.308 Yrs		
Strategy 3 HPV Primary + LBC Reflex	14.2K skr	1.4K skr	29.605 Yrs	0.297 Yrs	ICER 4.74K

Table 4 Cost effectiveness output when the dominated strategy 2 is excluded

An interpretation of this table would be that introducing the changes in the screening program suggested by strategy three would, according to our model, lead to an average increase in the expected discounted life years of 0.297 years. This would also lead to an increase of spending for the screening program of approximately 1400 sek on average for every woman. The ICER is approximately 4740 sek/life year. This number is well below the threshold value of 593000, derived from the WTP calculation in section 3.2.

The conclusion from the base cost effectiveness analysis is that the introduction of strategy three, primary screening for HPV and reflex cytological test using the LBC method is cost effective.

6.2 Sensitivity Analysis

When building a quantitative model and using this model for making decisions, it is important to study the robustness of the conclusions. A sensitivity analysis could be undertaken mainly for three reasons. (Meltzer 2001)

1. Help the decision maker in coping with uncertainty when trying to make the best decision with the current available information
2. Identify the sources of uncertainty for further differentiation and identification of relevant subgroups that differ from the base case analysis.
3. Identify where future efforts should be taken for finding additional information to reduce the uncertainty.

Our model is deterministic. This means that the input parameters are used with their expected value in the base analysis. This approach differs from a stochastic cost effectiveness analysis where the uncertainty concerning the parameters are built into the model by assigning different distributions to every parameter and reiterate the simulation many times. Therefore, we have to guess which parameters to choose when conducting the sensitivity analysis.

The interesting question is whether any of the reasonable changes in the model parameters changes the conclusion of the model; which in our case is that strategy three

is cost effective. If that is the case, these parameters and the uncertainty concerning their true values could be further studied in future research.

The effect parameters we choose to include and their respective range are presented in table 5.

Variables included in sensitivity analysis	Base value	Range
Sensitivity Cytology	0,78	0,6-0,85
Sensitivity LBC Cytology	0,89	0,78-1,00
Lab cost HPV Test	SEK 300	300-600
HPV prevalence	Table value	+-25%
HPV Regress rate to Well	Table value	+-50%
Discount factor Life Years	0,03	0,01-0,05
Discount factor Costs	0,03	0,01-0,05

Table 5 The parameters tested in sensitivity analysis

We will study if alterations to the parameters that favor the effect of the current practice, which is conventional screening, ceteris paribus will change the conclusion of the model. This is called univariate or one-way sensitivity analysis. However, changes can also be made simultaneously to several variables. This is called multivariate sensitivity analysis. In TreeAge Data Pro, multivariate sensitivity analysis can be made with up to three variables at the same time. A threshold value per unit of effectiveness is chosen, and the graph is filled with the strategy that is cost effective, given the different values of the variables.

First, we check the cost effectiveness robustness to changes in the discount rate. For this, a two way sensitivity analysis is chosen. The results can be shown in figure.14.

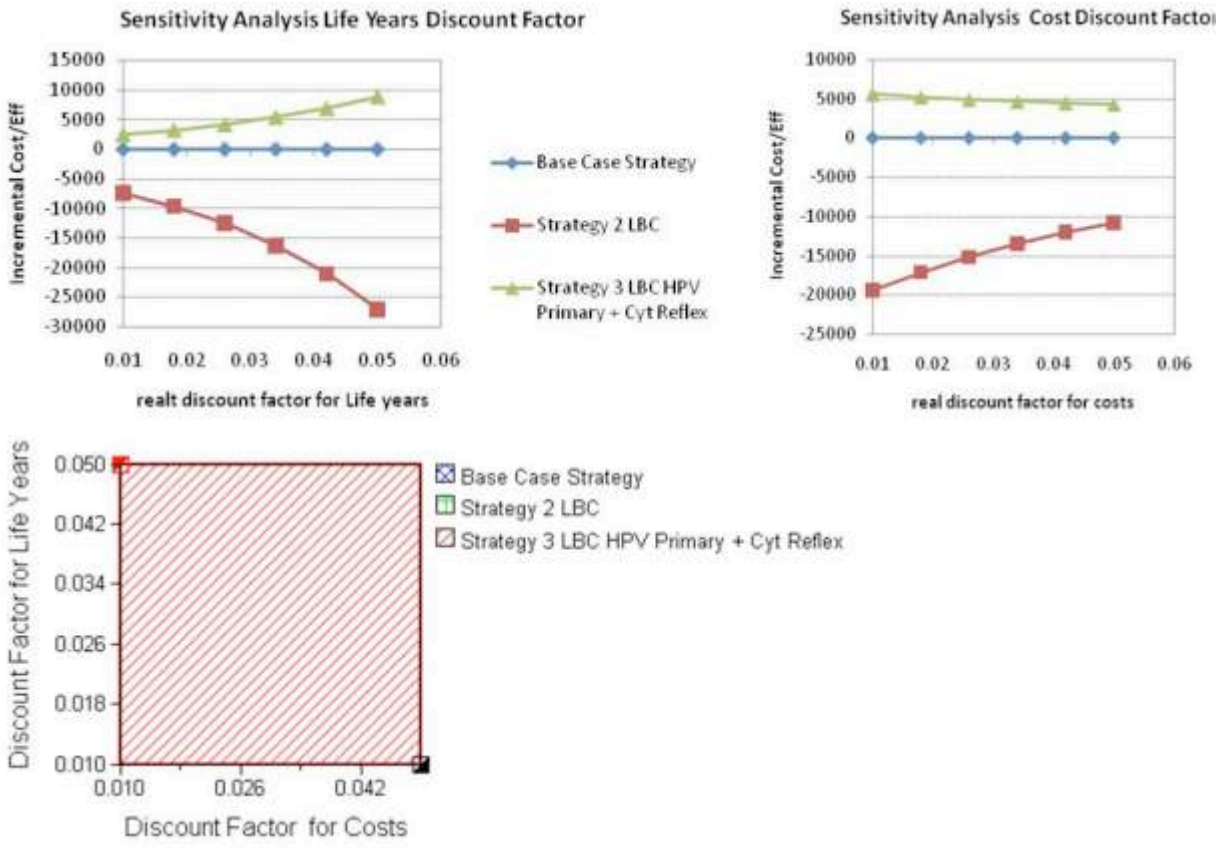


Figure 14 Two 1-way sensitivity analysis and finally one 2-way sensitivity analysis.. The ICER for strategy three never crosses the threshold value of 572 000 SEK.

When a 3-way sensitivity analysis is performed, two variables are visualized through the x- and y-axis and the third through an animation. A snapshot of this can be seen in figure 15, which tests if the ICER for strategy three passes the threshold value of 500000 sek. The sensitivity of ordinary cytology, LBC, and the cost of a HPV DNA lab analysis, are varied according to each specific range. In this specific snapshot, the cost of the DNA analysis is increased with 100 per cent (600 sek), compared with the base analysis value

(300 kr).

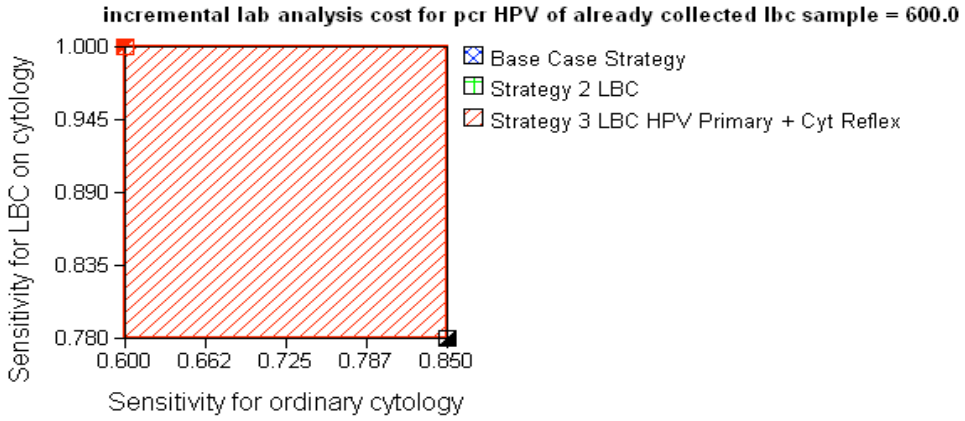


Figure 15 A snapshot of a multivariate sensitivity analysis testing the sensitivity of cytology, LBC and the marginal cost of HPV DNA analysis and their combined effect of the cost effectiveness of the three strategies

As can be seen from figure 15, even if conventional cytology is assigned its maximum effect value (0.85) and LBC its minimum (0.78) and the cost of HPV screening is doubled (600), strategy three never crosses the threshold value of 500000 sek for the ICER, since the whole area is covered by strategy three..

Some have argued that primary screening for HPV for women younger than thirty years old could have a detrimental effect on the cost effectiveness of this method, due to the high prevalence of HVP infections in this age group. They also point to the fact that the infections will self regress back to a healthy state, in clear majority of cases. (Strander et al 2007B) In our model, the HPV prevalence data is taken from Denmark. These numbers are probably higher than the Swedish context but it is interesting to see what happens to the cost effectiveness of HPV primary screening when the prevalence of HPV before the age of 30 is increased further. Therefore it is varied both + and – 50 percent in figure 16 in a 1-way analysis. The changes to the ICER are summarized in

table 6.

Change in HPV prevalence	Strategy	Cost	Eff	Incr C/E (ICER)
-50%	Base Case S	10K skr	29.549 Yrs	
	Strategy 3 I	11K skr	29.730 Yrs	ICER 5.18K
-25%	Base Case S	11K skr	29.417 Yrs	
	Strategy 3 I	13K skr	29.662 Yrs	ICER 4.89K
0%	Base Case S	13K skr	29.308 Yrs	
	Strategy 3 I	14K skr	29.605 Yrs	ICER 4.74K
+25%	Base Case S	14K skr	29.217 Yrs	
	Strategy 3 I	15K skr	29.556 Yrs	ICER 4.65K
+50%	Base Case S	15K skr	29.139 Yrs	
	Strategy 3 I	16K skr	29.515 Yrs	ICER 4.59K

Table 6 The ICER for strategy 3 decreases as the prevalence of HPV increases

The intuition behind this result can be that as the prevalence of HPV increases, it becomes even more relevant to identify these women at risk of developing CIN2/3 and in the future cervical cancer. The current screening does not look for the HPV status of women and if the HPV prevalence increases, it is expected that the expected discounted life years should decrease, in this case from 23.308 to 23.139 years.

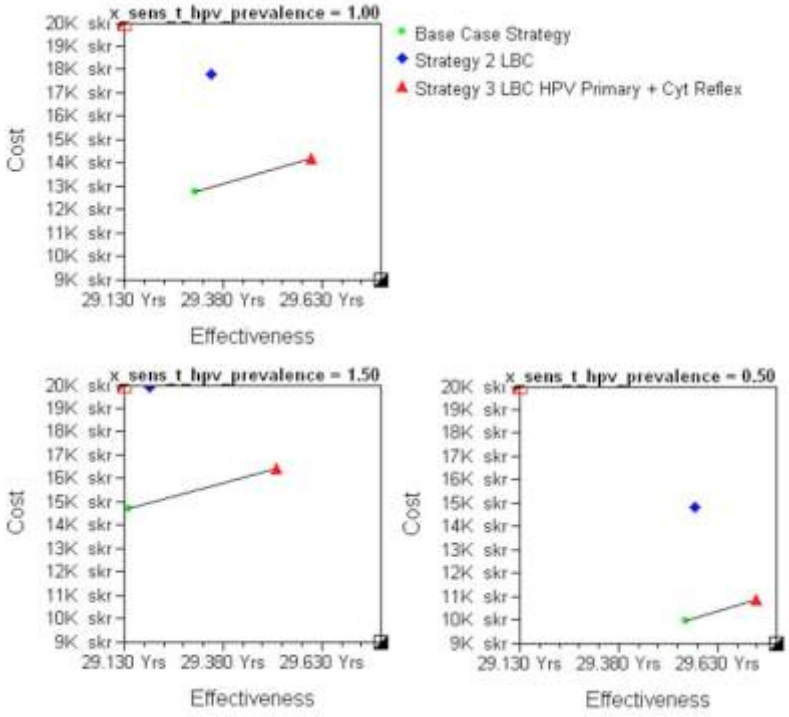


Figure 16 1-way sensitivity analysis of the cost effectiveness when the prevalence of HPV infections are varied +- 50 percent.

It is also interesting to look at a three way sensitivity analysis with the prevalence of HPV, the self regress ratio from HPV infected to well and finally the marginal cost of HPV DNA analysis, and their effect on the ICER for strategy three. This can be seen in figure 17. Even if the self regress factor is increased by 25 percent, the lab cost increased by 100 per cent and the prevalence of HPV, decreased by 50 per cent, the conclusion still stands. Strategy three is cost effective.

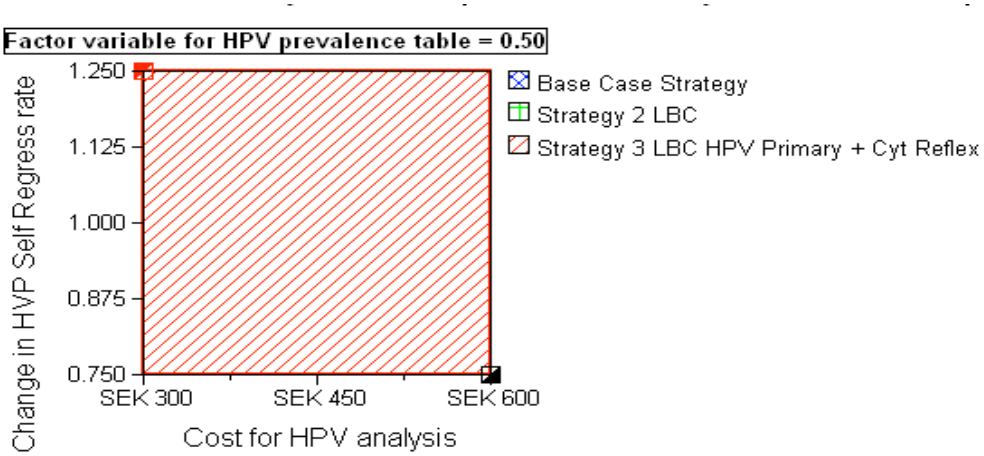


Figure 17 A snapshot of a multivariate sensitivity analysis testing the cost effectiveness conclusion when changing the assumptions concerning HPV epidemiology.

7 Conclusion

To conclude, the result that implementing primary screening for HPV with a reflex cytological test for every positive sample, even at an age of 23, would be cost effective seems to be robust.

This thesis set out to investigate whether new investment in screening practices could be motivated in terms of cost effectiveness, from a societal perspective. With the results from our model, we can conclude that introducing HPV-DNA testing as primary screening with reflex testing using LBC would indeed be cost effective and increase the effect in terms of lowered incidence and mortality of cervical cancer within the screened population.

8 Limitations and further research

8.1 Limitations

The conclusions from the markov model seem to be robust under sensitivity analysis. However, it is impossible to test every parameter and change every assumption in such a complex model. A Monte Carlo simulation would have been interesting to add to the analysis, given the availability of the data needed for that.

Also, due to lack of data, the cost and effect of changes in morbidity is not taken into account in the model. Hopefully, these two effects cancel out each other in the cost effectiveness.

8.2 Further research

There is a reported overuse of cytological testing within specific groups. Many women attend a midwife or gynecologist outside the organized program and are then tested with so called opportunistic screening. There are many possible reasons for this. One reason could be that women over the age of 60 are not included in the organized program but still feel the need to check their status. It would be interesting to check whether an introduction of a more sensitive test, such as HPV-DNA screening would have an effect on these women's attitude towards opportunistic screening.

It would also be interesting to study how the long term expected decrease in HPV prevalence, due to the introduction of two specific vaccines targeted at two strands of the virus, will affect the cost effectiveness of the screening program. It will probably decrease the marginal effect for the women participating in the screening.

9 References

9.1 Textbook

Drummond, M., Sculpher, M., Torrance, G., O`Brien, B., and Stoddart, G. (2005), *Methods for the Economic Evaluation of Health Care Programmes*. New York: Oxford University Press.

Gold, M., Siegel, J., Russell, L., and Weinstein, M. (1996), *Cost-effectiveness in health and medicine*. New York: Oxford University Press.

Strander, B. (2008), *Cervical cancer prevention. Studies on possible improvements*. Doctoral Thesis. Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, Göteborg University.

9.2 Articles

Andrae, B., Kemetli, L., Sparen, P., et al. (2008), "Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden". *J Natl Cancer Inst,* 100, 1-8.

Arbyn, M., Sasieni, P., Meijer, Ch., J., et al. (2006), "Clinical applications of HPV testing: a summary of meta-analyses". *Vaccine*, 24 (suppl 3), 78-79.

Bistoletti, P., Ellström A., Dillner, J., et al. (2005), "Screening för cervixcancer kan vara kostnadseffektiv. Kombinationen cellprov och HPV-test skulle ge ytterligare vinster." *Läkartidningen*, 102, 1874-1879.

Bosch, FX., Lorincz, A., Munoz, N., et al (2002), "The causal relation between human papillomavirus and cervical cancer". *J Clin Pathol*, 55, 244-265.

Andersson (2003), "HPV-test säkrare än cellprov för att avslöja cervixcancer", Dagens Medicin 6 november.

Davey, E., d'Assuncao, J., Irwig, L., Macaskill, P., et al. (2007), "Accuracy of reading liquid based cytology slides using the ThinPrep Imager compared with conventional cytology: prospective study". *BMJ*, 335(31), 1-8.

Dillner, J.(2000), ”Cervical cancer screening in Sweden”. *Eur J Cancer* , 36, 2255-2259.

Elfgren, K., Bistoletti, P., Dillner, L, et al. (1996), ”Conization for cervical intraepithelial neoplasia is followed by disappearance of human papillomavirus deoxyribonucleic acid and a decline in serum and cervical mucus antibodies against human papillomavirus antigens”. *Am J Obstet Gynecol*, March, 937-942.

Forslund, O., Antonsson, A., Edlund, K., et al. (2002), ”Population-based type-specific prevalence of high-risk human papillomavirus infection in middle-aged Swedish women”. *J Med Virol*, 66(4), 535-541.

Goldie, SJ, Kim, J., Wright, TC. (2004), “Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more”. *Obstet Gynecol*, 103, 619-631.

Johannesson, M., Meltzer, D. (1998), “Some reflections on cost-effectiveness analysis”. *Health Econ*, 7, 1-7.

Johannesson, M., Meltzer, D., and O¨Conor, R. (1997), “Incorporating future costs in medical cost-effectiveness analysis: implications for the cost-effectiveness of the treatment of hypertension”. *Med Decis Making*, 17(4), 382-389.

Karlsson, G. and Johannesson, M. (1996), “The decision rules on cost-effectiveness analysis”. *Pharmacoeconomics*, 9(2), 113-120.

Kim, J., Wright, T., and Goldie, S.J., (2005), “Cost-effectiveness of Human Papillomavirus DNA testing in the United Kingdom, the Netherlands, France, and Italy”. *Cancer Inst*, 97, 888-895.

Kobelt, G. (2002), *Health economics: An Introduction to Economic Evaluations.* Office of Health Economics, Whitehall, London.

Mayrand, M-H., Duarte-Franco, E, et al.(2007), ”Human Papillomavirus DNA versus Papanicolau Screening Tests for Cervical Cancer”. *The New England Journal of Medicine*, 357(16), 1579-1588.

Meltzer, D. (1997) “Accounting for future costs in medical cost effectiveness analysis” *Journal of Health Economics,* 16, 33-64.

Meltzer, D. (2001), ”Adresssing uncertainty in medical cost effectiveness analysis”. *Journal of Health Economics* 20, 109-129.

Nationellt Kvalitetsregister för Gynekologisk Cellprovskontroll. *Gynekologisk cellprovskontroll i Sverige*. Report from 2007. Karolinska Institutet, Stockholm.

National Institute for Clinical Excellence. (2000), "Guidance on the use of liquid-based cytology for cervical screening". *NICE Technology Appraisal Guidance*. London: National Institute for Clinical Excellence.

Nobbenhuis, M. A., Meijer, C., van den brule, A., et al. (2001), "Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia". *Br J C*, 84(6), 796-801.

Näslund, I. (1985), "Evaluation of screening procedures for uterine cervical carcinoma". Stockholm: Karolinska Institutet.

Näslund, I., Auer, G., Pettersson, F., Sjövall, K. (1986), Evaluation of the pulse wash sampling technique for screening of uterine cervical carcinoma. Acta Radiol Oncol, 25(2), 131-136.

O'Brien, B. J., Drummond, M. F., Labelle, R. J., Willan, A. (1994), "In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care". *Medical Care,* 32(2), 150-163.

Paraskevaidis, E., Arbyn, M., Sotiriadis, A. (2004), "The roll of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature". *Cancer Treatment Reviews*, 30, 205-211.

Plummer, M., Schiffman, M., Castle, Ph., Maucort-Boulch, D., et al. (2007), "A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion", *J Infec Dis*, june 1, 195, 1582-1589.

Ponten, J., Adami, H., Bergstrom, R., et al. (1995), "Strategies for global control of cervical cancer". *Intl J of Cancer,* 60*,* 1-26.

Richart, R., and Barron, B. (1969), "A follow-up study of patients with cervical dysplasia". *Am J Obstet Cynecol.* 105(3), 386-393.

Ronco, G., Giorgi-Rossi, P., Carozzi, F., et al. (2006), "Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial". *Lancet Oncol*, june 14, 547-555.

Rylander, E., Rådberg, T. (1997), ”Att förebygga cervixcancer samt vaginal och vulvacancer. Riktlinjer för diagnos, behandling och kontroll av intraepithelial neoplasi och papillomvirusinfectioner i cervix, vagina och vulva”. Svensk förening för Obstetrik och Gynekologi Arbets & Referensgrupper (ARG) report, 34.

Schiffman, M. (2007), ”Integration of Human Papillomavirus Vaccination, Cytology, and Human Papillomavirus Testing”. *Cancer (Cancer Cytopathol)*, 111(3), 145-153.

Siegel, J., Weinstein M., Russel, L., and Gold, M. (1996), ”For the Panel on cost-effectiveness in health and medicine. Recommendations for reporting cost-effectiveness analyses”. *Journal of the American Medical Association*, 276; 1339-341

Siebert, U., Sroczynski, G., Hillemanns, P., et al. (2006), “The German Cervical Cancer Screening Model: development and validation of a decision-analytic model for cervical cancer screening in Germany”. European J Public Health, 16(2), 185-192.

Sonnenberg, M., and Beck, J.R. (1993), “Markov models in medical decision making: a practical guide”. *Med Decis Making*, 13(4), 321-339.

Strander, B., Andersson-Ellström, A., Milsom, I., et al. (2007),”Liquid-based Cytology versus Conventional Papanicolaou Smear in an organized screening programme”. Cancer (Cancer Cytopathology), October 25, 111(5), 285-291.

The National Board of Health and Welfare. *Cancer incidence in Sweden*. Stockholm: The National Board of Heath and Welfare – Center for epidemiology, 1958-2005.

The National Board of Health and Welfare. *Cancer i siffror 2005*. Stockholm: The National Board of Health and Welfare. Available [online]: www.cancerfonden.se [2008-08-13]

The National Board of Health and Welfare. *Gynekologisk cellprovskontroll – Förslag till screeningprogram* [Guidelines for cervical screening]. Stockholm: The National Board of Health and Welfare, 1998.

Weinstein, M. C., (1990) ”Principles of cost-effective resource allocation in health care organizations”. Int. J. Technol. Assess. Health Care 6, pp. 93–105

Östör, AG., (1993), ”Natural history of cervical intraepithelial neoplasia: a critical review”. *Intl J Gyn Pathol,* 12 (2), 186-192.

9.3 Interviews

Björn Strander, 24 April 2008, Gothenburg

Anders Hjerpe , 1 January 2008, Stockholm

Erik Wilander, 3 December 2007, Uppsala

Sonia Andersson, 13 November 2007, Stockholm

9.4 Other Sources

LFNAR 2003:2, *Läkemedelsförmånsnämndes allmänna råd om ekonomiska utvärderingar.* Available[online]: http://www.lfn.se/upload/Lagar_och_foreskrifter/LAG_lfnar2003-2.pdf [2008-08-14]

Statistisk årsbok 2007 Available [online]: *www.scb.se/**statistik**/_publikationer/ov0904_**2007**a01_br_a01sa0701.pdf* [2008-09-30]

Appendix

1 Markov Model Input parameters

2 Markov Model Tree Layout

1 Markov mode input parameters

A	B	C
Variables	**Name**	**Value**
1	cAlt_Cost_Death_Total	SEK 100 000,00
2	cAlt_Cost_Patient_h	SEK 440,44
3	cBiophsy_Colposcopy_Total	SEK 5 543,08
4	cBNP_Capita_2007	SEK 336 000,00
5	cConization_Med_Cost	SEK 5 000,00
6	cCytTest_Total	SEK 595,44
7	cCyt_Med_Cost	SEK 155,00
8	cFollowUp_Physician	SEK 1 740,94
9	cLBC_CytTest_Total	SEK 639,94
10	cLBC_HPVTest	SEK 300,00
11	cLBC_Med_Cost	SEK 210,75
12	cMidwife_h	SEK 80,00
13	cOperation_CervixCancer_Total	SEK 14 045,40
14	cOperation_Conization_Total	SEK 8 725,52
15	cOperation_Inv_Cancer_Total	SEK 124 931,28
16	cPhysician_h	SEK 1 300,50
17	cPost_Cervix_Operation_Sick	SEK 28 000,00
18	cPost_Conization_Sick	SEK 0,00
19	cPost_InvasiveCancer_Sick	SEK 28 000,00
20	pCompliance_Bio_Colp	1
21	pCompliance_Conization	1
22	pCompliance_Cyt2_3_Conf	1
23	pCompliance_CytScreen	0,72
24	pCompliance_HPV_Conf	1
25	pCompliance_HPV_Neg	0,72
26	pMortality_CervixCancer	0,0756
27	pMortality_OtherCause	0.000280092 (Increasing with age)
28	pMortality_PostCancerOperation	0,03398878
29	pPrevalence_HPV_AgeAdj	0.39 (startvalue for 23 year women)
30	pProgress_Cervix_InvasiveCancer	0,2015
31	pProgress_PostConization_Cervix	0,1
32	pProgress_PostCervixOp_Cervix	0,1
33	pProgress_Well_HPV_perm	0,39
34	pRegress_CIN2_3_Well	0,1027
35	pScreening	1
36	pScreen_Cyt_Confirmed	1
37	pScreen_HPVNegConf	0
38	pScreen_HPV_Perm	1
39	pScreen_Post_Conization	1
40	pSensitivity_ColpBio_CervixCancer	1
41	pSensitivity_ColpBio_CIN2_3	0,7
42	pSensitivity_Cyt_CervixCancer	0,833

A	B	C
43	pSensitivity_Cyt_Cyt	0,78
44	pSensitivity_LBC_Cervix	0,833
45	pSensitivity_LBC_Cyt	0,89
46	pSensitivity_LBC_HPV	0,95
47	pSpecifCyt_Cyt	0,92
48	pSpecifCyt_HPV	1
49	pSpecifLBC_Cyt	0,78
50	pSpecifLBC_HPV	0,698
51	pSpecif_Colp_Biosc	0,98
52	pSymptoms_CervixCancer	0,19
53	pSymptoms_InvasiveCancer	0,75
54	startAge	23
55	x_DiscountFactor_Cost	0,03
56	x_DiscountFactor_Life	0,03
57	x_ExpLifeYearsLeft_Average	25
58	x_ExpLifeYearsLeft_Cervix_Cancer	11
59	x_ExpLifeYearsLeft_Cin	18
60	x_ExpLifeYearsLeft_InvCancer	9
61	x_ExpLifeYearsLeft_PostCon	21
62	x_ExpLifeYrsLeft_Post_Cancer	15
63	x_InfRate	1,02

A	B
Variable	**Definition Info**
1	Arbitrarily chosen. Not used in base analysis.
2	bnp/hour worked 2007. Source SCB Nationalrakenskaper
3	Direct material is taken from average of Ellinor and Bistolletti 2005. Therefore it is adjusted for two years of inflation
4	source: scb.se "statistisk årsbok 2007"
5	Source Bistolletti et al 2005 Note that this is an average of two datapoints.
6	Our calculation
7	average of two values: unpublished calculations by Andersson, Karin and Hjerpe, Anders
8	Our calculation
9	Our calculation
10	Value varies depending on the lab that does the analysis. Source Strander estimation in interview 2008.
11	Source Average of two datapoints, unpublished calculations by Andersson and Hjerpe 2008.
12	Source Estimation from interview with Wilander 2007.
13	Source; Bistolletti 2005. Therefore data is adjusted for two years of inflation.
14	Source Bistolletti 2005 and Ellinor. adjusted for two years of inflation.
15	Source; Bistolletti 2005. Therefore adjusted for two years of inflation.
16	Source Bistolletti 2005. Therefore adjusted for two years of inflaiton.
17	Assumption that post operation sick leave is one month on average. Only included in sensitivity analysis.
18	Source. Bjorn Strander orally at interview.
19	Assumption that post operation sick leave is one month. Only included in sensitivity analysis
20	Assumption.
21	Assumption
22	Assumption

23	Source Average in Sweden from latest "Kvalitetsregister 2007". Note that this number is for age category 23-50. In reality, women over 50 have higher compliance, although not taken into account in this model.	
24	Assumption	
25	Assumption. Should intuitively be the same as conventional cytological compliance.	
26	Source Cancer i siffror 2005. Adjusted from five year risk to one year risk	
27	age specific survival curve from 23 to 60. Source: SCB.	
28	Source Socialstyrelsen pdf "utdrag dodsorsaker". The source value is increased 10 year risk of dying, therefore adjusted for one year risk by dividing this aggregaded risk by 10.	
29	Source Kaersten 2006	
30	Source Siebert et al 2006.p.184	
31	Source strander et al 2007.	
32	Assumtion. Lack of specific data. Instead same number as pProgress_PostConization_Cervix	
33	pPrevalence_HPV_AgeAdj	
34	source siebert et al 2006 p.187	
35	Binary probability of ordinary screening offer for women not diagnosed with HPV neg or post treated.	
36	Strander 2008	
37	Assumption. Conditional one year probability of screening patients already confirmed to be HPV negative . First six years, no additional screening offer.	
38	Assumption. Conditional Screening Probability of already confirmed last year patients. Yearly screening first three years due to the fact that only after two years the real persistent infections can be spotted.	
39	Source bistolletti 2005. Conditional one year prob of patients already treated for CIN2/3	
40	Assumption.	
41	source Coupe et al 2006 p.419	
42	See Strander 2008 p.48.Note that this value is really for follow up of CIN2/3 treatment, not when prevalence of Cervical Cancer is 100 percent, which it is by definition here.	

A	B
43	Source Strander 2008, Coupe et al 2007, BJOG 2007;114:416–424. pp. 419 Note that there is a large difference between different estimate of this number. However, to be conservative, we choose a relatively high number in our base analysis
44	Assumed to be same value as psens cyt cervix.
45	See Strander 2008 p.29-32. and goldie 2004, and davey et al 2007 p.6
46	coupe et al 2007 pp.419
47	1-the level of uncertain samples. See "Gynekologiskt kvalitetsregister 2007".
48	Obiosly one since no probability for false positive
49	Lack of data. Probably lower than conventional cytology. In base analysis lower than cyt.
50	Shiffman et al 2005 p.148 middle paragraph. Note thas many numbers are present. This value should be lower than cyt however
51	Assumed to be almost unity. Simplification that is ok, according to Strander.
52	source goldie et al 2004 p. 621
53	source Goldie et al 2004 p. 621.
54	Age when screening starts
55	Source Drummond et al 2005 pp.111. Varied from 0.00-0.05 in sensitivity analysis.
56	Source Drummond et al 2005 pp.111. Varied from 0.00-0.05 in sensitivity analysis.
57	Source SCB Livslangdtabell 2007. Expected Life Years for 60 year old women.
58	Arbitrarily chosen. Should be higher than invasive cancer
59	Arbitrarily chosen. Should be lower than post conization state.
60	Arbitrarily chosen. Has to be less than state well, cin, post con or cancer treatment,
61	Arbitrarily chosen. Should be next most highest after average
62	Arbitrarily chosen. Has to be higher than untreated cervix cancer (10)but lower than average for all (25)
63	average inflation rate for 2005 and 2006. Used for some older nominal costs.

Variable	Formula
1	d_NonDir_MedCost*cPalliative_Care
2	
3	d_Dir_MedCost*(3654.50*1.02^2+cPhysician_h)+d_Dir_NonMedCost*cAlt_Cost_Patient_h
4	
5	
6	d_Dir_MedCost*(cCyt_Med_Cost)+d_Dir_NonMedCost*cAlt_Cost_Patient_h
7	
8	cAlt_Cost_Patient_h+cPhysician_h
9	d_Dir_MedCost*(cLBC_Med_Cost)+d_Dir_NonMedCost*cAlt_Cost_Patient_h
10	
11	
12	
13	d_Dir_MedCost*(13500*1.02^2)+d_NonDir_NonMedCost*cPost_Cervix_Operation_Sick
14	d_Dir_MedCost*(cConization_Med_Cost*x_InfRate^2)+d_Dir_NonMedCost*cAlt_Cost_Patient_h*8+d_NonDir_NonMedCost*cPost_Conization_Sick
15	d_Dir_MedCost*(115000*x_InfRate^2)+d_Dir_NonMedCost*cAlt_Cost_Patient_h*12+d_NonDir_NonMedCost*cPost_InvasiveCancer_Sick
16	1250*1.02^2
17	cBNP_Capita_2007/12
18	
19	cBNP_Capita_2007/12
20	
21	
22	
23	
24	
25	
26	(1+x)^5=0.67.5 1+x= 0.675^1/5 x = 0.675^1/5-1 = -0.0756 per year or 7.56 %
27	(1-tSurvivalAgeSpec[Age+1])/tSurvivalAgeSpec[Age]
28	
29	tHPVprevalens[Age]
30	
31	
32	
33	
34	If(age<35;0.0173;0.0595)
35	If(_stage=0;1;0)|IF(_stage=3;1;0)|If(_stage=6;1;0)|IF(_stage=9;1;0)|If(_stage=12;1;0)|IF(_stage=15;1;0)|If(_stage=18;1;0)|IF(_stage=21;1;0)|If(_stage=24;1;0)|IF(_stage=27;1;0)|If(_stage=32;1;0)|IF(_stage=37;1;0)
36	
37	If(_tunnel>=6;1;0)
38	If(_tunnel<=3;1;pScreening)
39	If(age<35;0.1027;0.0645)

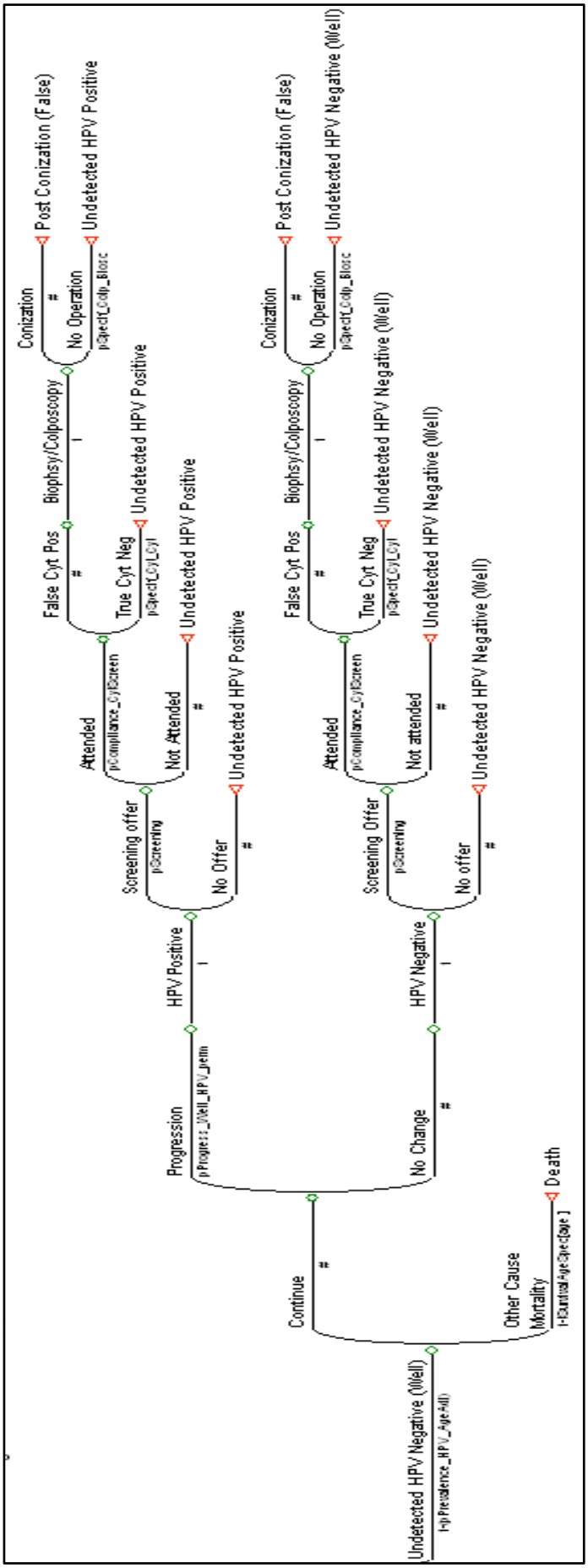
Tables	Name	Value
1	tHPVprevalence	0,59 (20-24 yy) 0,27 (25-29 yy) 0,15 (30-39 yy) 0,08 (40-49 yy) 0,06 (50-59 yy) 0,04 (60-69 yy)
2	tRegress_HPV_Well	0.67 (tunnel 0.5)
		0.48 (tunnel 1)
		0.38(tunnel 1.5)
4	tProgress_PostCon_CIN2_3	0.1(tunnel 1)
		0.05(tunnel 10)
		0.01(tunnel 25)
5	tProgress_PostCon_Cervix	0.0000328(tunnel 1.5)
		0.000027(tunnel 3)
		0.0000261(tunnel 7)
		0.0000223(tunnel 12)
		0.0000184(tunnel 17)
		0.0000173(tunnel 22.5)
		0.0000172(tunnel 25)
6	tProgressCIN2_3_CervixCancer	0.0015(tunnel 1)
		0.002324(tunnel 2)
		0.094(tunnel 7)
		0.01(tunnel 10)
		0.02(tunnel 37)
7	tProgress_HPV_CIN2_3	0.0173(tunnel 1)
		0.0173(tunnel 2)
		0.05(tunnel 3)
		0.1(tunnel 4)
		0.2(tunnel 5)
		0.2(tunnel 6)
		0.2(tunnel 7)
		0.3(tunnel 8)
		0.4(tunnel 9)
		0.5(tunnel 10)

	Definition Info
1	Source Kaersten 2006. Note that this data is for a danish context. This is due to a lack of data for Sweden, however Denmark should suffice as a god proxy for Sweden in terms of HPV prevalence, according to Sparen 2008 (interview)
2	Source Plummer et al 2007
4	Source Source Coupe et al 2006 p. 419. for first year prob. Then arbitrarily decreased for specific _tunnel values.
5	Source strander et al 2007. table for probability of progress from conizationed to cervix cancer using _tunnel as counter.
6	Source Source Basevalue is from Bisttolleti 2007. Value two from Siebert et al 2007 Value seven from Coupe et al 2006. Note that value two and seven are one year probabilities, although their large difference from Bisttolletti 2007.
7	Source Ponten et al 1995 p.6 for basevalue probability of going from HPV Positive to CIN2 3, given how many years spent in the state, our adjustment. Using the tunnel counter for increasing the value from the index.

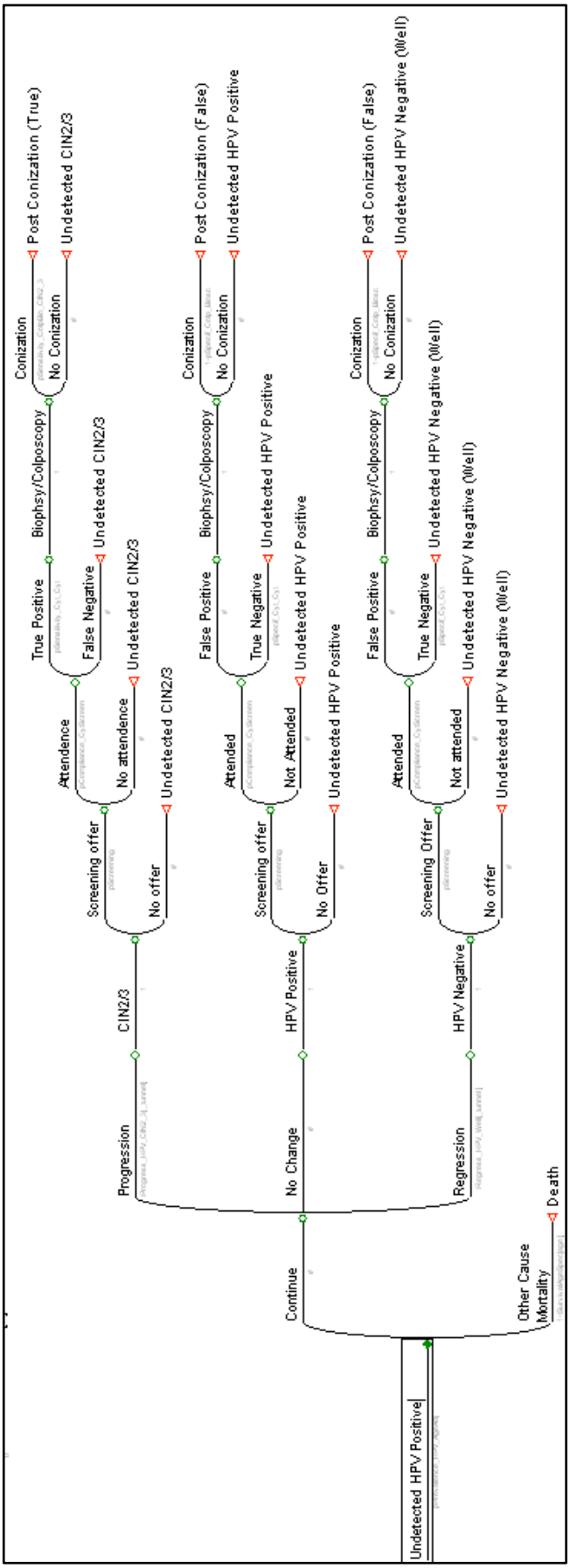
2 Markov Model Tree Layout

As can be seen from the cycle tree representation in 5.2, figur, there are a total of thirteen states in the markov model. The detected states have all two versions, true and false, due to the fact that no screening method has perfect 100 per cent specificity and sensitivity. This leads to false positive and negative cases. If the model did not discriminate between a false and a true result from a screening test the resulting effectiveness measure would be hard to calculate, and even harder to interpret.

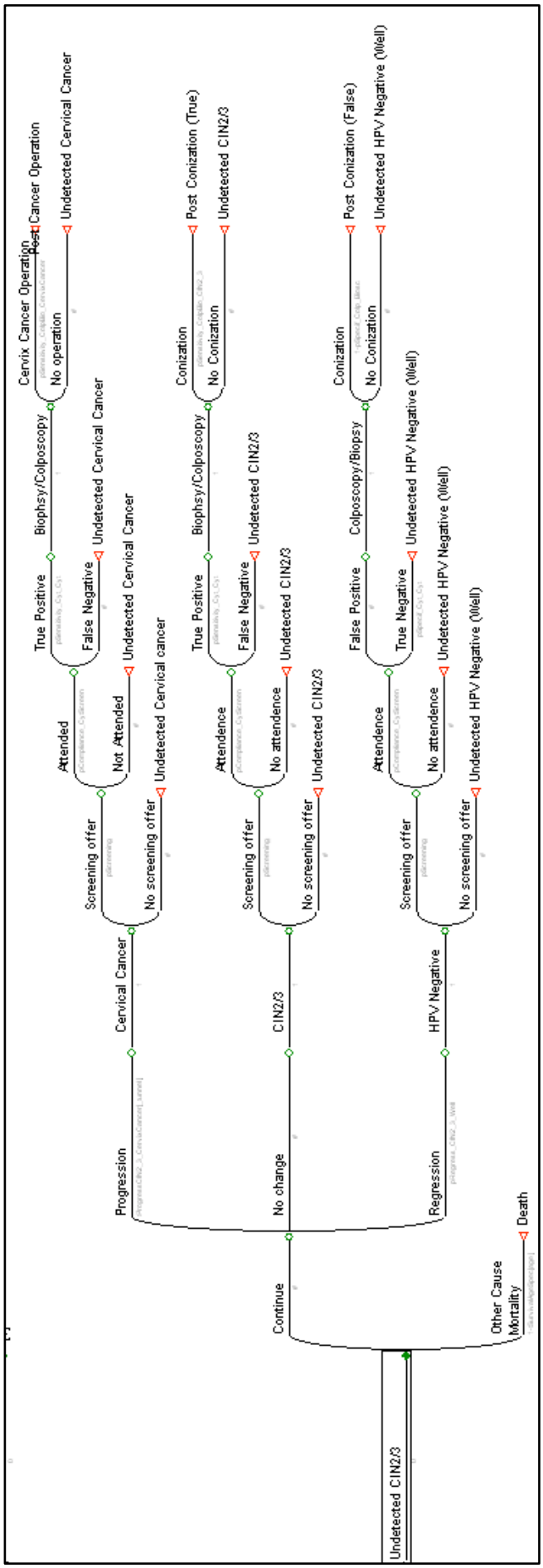
The undetected stages do not have two versions, since no test by definition has taken place in this group. Hence, the possibility of a false designation is zero.



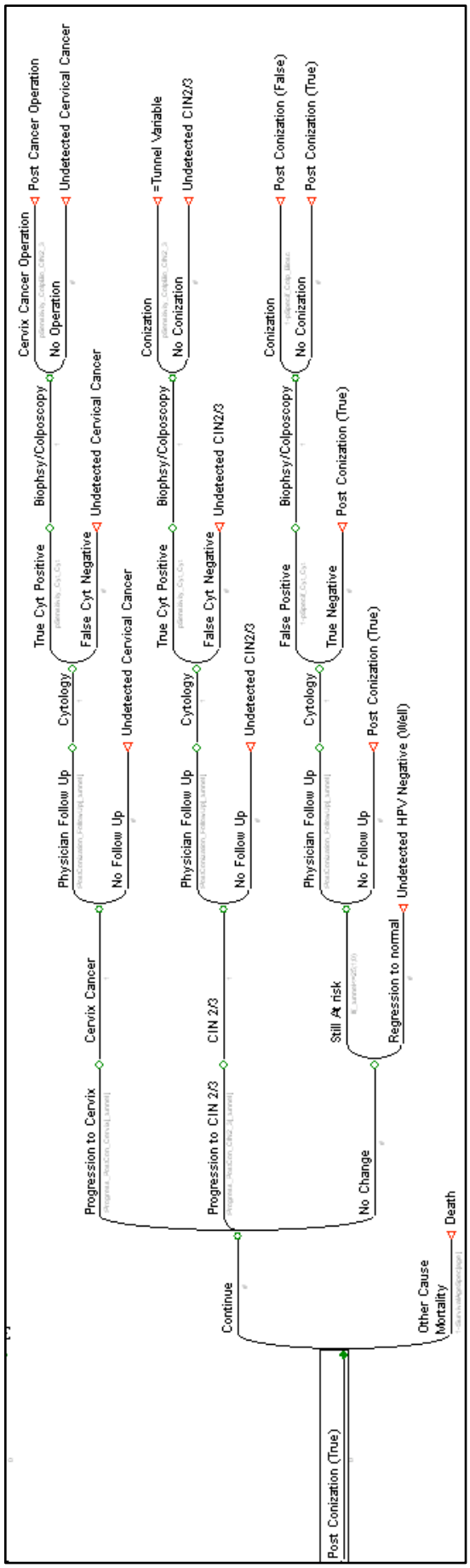
Healthy State



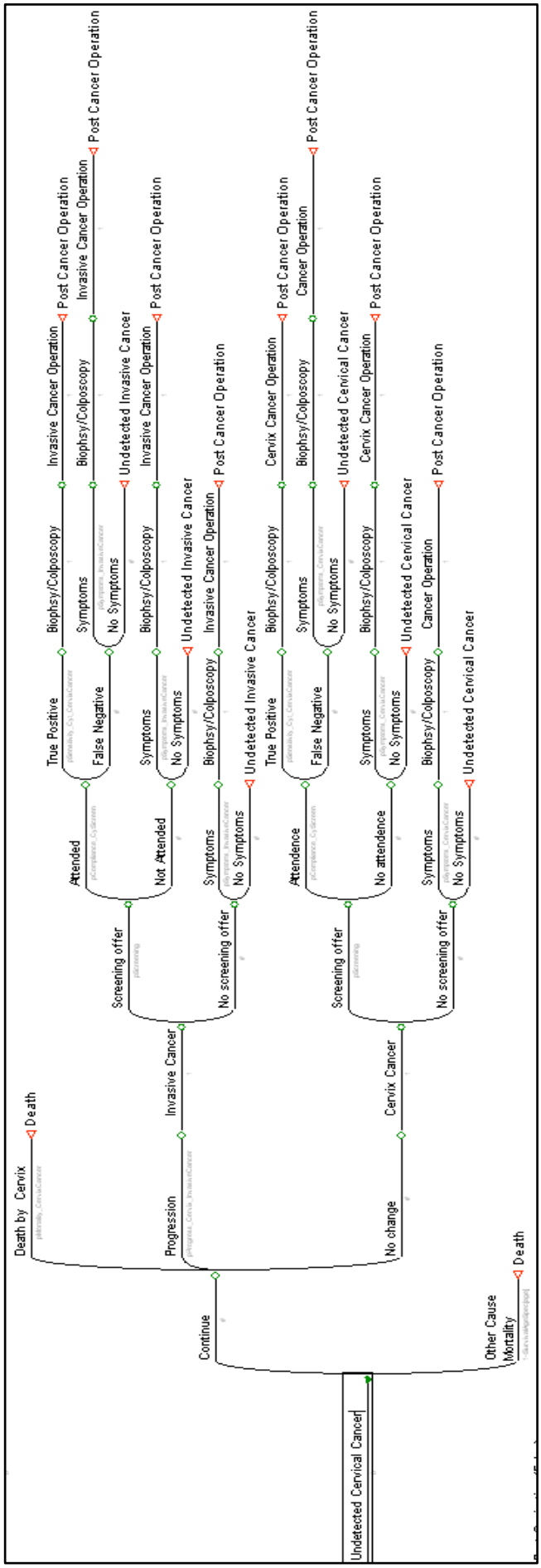
Undetected HPV Positive State



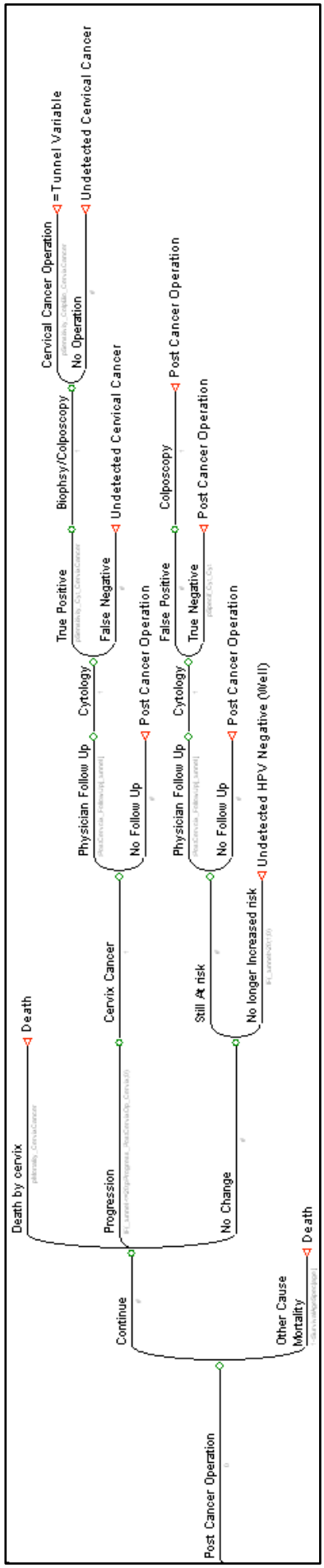
Undetected CIN2/3 State



Post Conization State



Undetected Cervix Cancer State



Post Cancer Treatment State