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HEALTH ECONOMICS OF BREAST CANCER

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Stockholm 2007
You’re going to juggle eggs? It’s a metaphor for life. Each egg represents one of life’s concerns. The goal is to devote each the appropriate amount of individual attention while simultaneously nurturing and guiding all the others.

Life is about balance and staying cool and alert as everything threatens to spin out of control.

And sometimes we make a big mess of things. But the important thing is persistence.
ABSTRACT

Breast cancer is a major cause of morbidity and mortality. Resources are spent in order to prevent, diagnose, and treat breast cancer. Since health care resources are limited, these resources must be allocated in an optimal way in order to maximise health. Currently, there are several different interventions available for breast cancer, and new interventions are under development. As new technologies are developed, it is important to evaluate if these new technologies produce improvements in health at an acceptable cost compared to the older technologies. The purpose of this thesis was to contribute to the development in health economics of breast cancer. The specific aspects addressed were the cost of illness of breast cancer, the cost and quality of life in different states of breast cancer, and economic evaluations of breast cancer interventions.

The cost of illness of breast cancer in Sweden was estimated using a prevalence based top-down approach. The total cost of breast cancer in 2002 in Sweden was estimated to approximately 3 billion SEK. Direct costs accounted for about 30% of the total cost, with indirect costs accounting for the remaining 70%. For direct costs, the main cost item was hospitalisation, followed by outpatient visits. For indirect costs, productivity losses due to mortality was the main cost driver.

Resource use, cost and health related quality of life in different states of breast cancer were estimated based on a naturalistic observational study. Breast cancer was found to be associated with both substantial direct and indirect costs. The total cost was found to be higher for patients in their first year after primary breast cancer, for patients in their first year after a recurrence, and for patients with metastatic disease compared to patients in their second and following years after a primary breast cancer or recurrence. For patients aged less than 65, indirect costs accounted for a majority of the total cost. The study also found breast cancer to be associated with a reduction of the health related quality of life. This reduction was most pronounced for patients with metastatic disease. For all the different disease states, this reduction seems to be driven by pain and discomfort as well as anxiety and depression.

Two computer simulation models were developed to project costs and benefits for treatments of breast cancer in the metastatic setting and the adjuvant setting respectively. Health economic data collected in the naturalistic observational study were used in the models. The cost-effectiveness of trastuzumab and chemotherapy compared to chemotherapy alone was estimated for Swedish women with metastatic breast cancer. In the adjuvant setting, the cost effectiveness of one year of adjuvant trastuzumab after adjuvant chemotherapy compared to adjuvant chemotherapy alone was estimated. In both the metastatic and the adjuvant setting, the addition of trastuzumab was found to be cost-effective.

This thesis presents new information about the economic burden of breast cancer, as well as new data on the cost and quality of life for patients in different states of breast cancer. These data represent an important input for economic evaluations of breast cancer interventions, and will improve future economic evaluations of breast cancer. The economic evaluations presented in this thesis can be used for informed decisions about resource allocation for patients with breast cancer within the healthcare system.
LIST OF PUBLICATIONS

This thesis is based on the following original papers, which will be referred to by their Roman numerals:


*Keywords:* breast cancer, cost of illness, cost, quality of life, economic evaluation, cost-effectiveness, modeling
**LIST OF ABBREVIATIONS**

<table>
<thead>
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<th>Description</th>
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<tr>
<td>CMA</td>
<td>Cost-minimisation analysis</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis</td>
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<tr>
<td>CUA</td>
<td>Cost utility analysis</td>
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<tr>
<td>CBA</td>
<td>Cost benefit analysis</td>
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<tr>
<td>DALY</td>
<td>Disability adjusted life-year</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FISH</td>
<td>Fluorescence in situ hybridization</td>
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<tr>
<td>GDP</td>
<td>Gross domestic product</td>
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<tr>
<td>HER2</td>
<td>Human epidermal growth factor receptor-2</td>
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<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<td>IHC</td>
<td>Immunohistochemical</td>
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<td>LY</td>
<td>Life years</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
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<tr>
<td>QAPFY</td>
<td>Quality adjusted progression free years</td>
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<tr>
<td>SERM</td>
<td>Selective Estrogen Receptor Modulator</td>
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<tr>
<td>SG</td>
<td>Standard gamble</td>
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<tr>
<td>TTO</td>
<td>Time trade off</td>
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<td>TTP</td>
<td>Time to progression</td>
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<tr>
<td>WTP</td>
<td>Willingness to pay</td>
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1 INTRODUCTION
Breast cancer is a major cause of morbidity and mortality. Resources are spent in order to prevent, diagnose, and treat breast cancer. Since our resources are limited, they must be allocated in an optimal way in order to maximise goals regarding the level and distribution of health of the population served. Currently, there are many different interventions available for breast cancer patients, preventive, diagnostic and therapeutic, and new interventions are always under development. As new technologies are to be used, it is important to evaluate if these new technologies produce improvements in health at an acceptable cost compared to the older technologies. The growing demand for efficient use of resources has made health economic studies an increasingly important tool for assisting in decisions about resource allocation within the health care system.

This thesis studies aspects of the health economics of breast cancer relevant for decisions about resource allocation within the health care system. These aspects are: the economic burden of breast cancer to society, the cost and quality of life associated with patients in different states of breast cancer, and economic evaluations of breast cancer interventions.
2 AIMS OF THE THESIS

The general purpose of this thesis was to study aspects of the health economics of breast cancer. Specifically, this thesis aims at:

Cost of illness of breast cancer (Paper I)
- To investigate the direct and indirect costs of breast cancer in Sweden using a top-down, prevalence based cost of illness approach.

Cost and quality of life associated with different states of breast cancer (Papers II-III)
- To assess the societal cost for patients in different states of breast cancer in Sweden.
- To assess the health related quality of life associated with different states of breast cancer.

Economic evaluation of breast cancer interventions (Papers IV-V)
- To develop simulation models for both early and metastatic breast cancer, predicting costs and outcomes for a hypothetical cohort of patients.
- To estimate the cost-effectiveness of trastuzumab for patients with early breast cancer as well as for patients with metastatic breast cancer.
3 BREAST CANCER

Cancer is caused by a multiplicity of genetic disturbances in somatic cells[1]. The genetic disturbances result in an uncontrolled growth of abnormal cells, giving rise to a malignant tumour. Tumour cells have the ability to spread either by direct growth to adjacent tissue (invasion) or by implantation into distant sites through the bloodstream or lymphatic system (metastasis)[2]. Breast cancer is defined as a malignant growth that begins in the epithelium of the breast.

3.1 INCIDENCE, PREVALENCE, AND MORTALITY

Breast cancer is the most frequent cancer of women (23% of all cancers), with an estimated 1.15 million new cases worldwide each year. More than half of the cases occur in industrialised countries with about 361 000 in Europe and 230 000 in North America[3]. In Sweden, approximately 7 000 new cases of breast cancer are diagnosed each year[4]. Incidence rates are high in most of the industrialised countries with the highest age-standardized incidence in North America (99.4 per 100 000)[3, 5]. The high incidence in industrialised countries could partly be due to screening programmes that detect early invasive cancers, some of which would otherwise have been diagnosed later or not at all[3, 6].

The prognosis of breast cancer is relatively good, with the age-adjusted survival in industrialised countries being 73%. However, despite this, breast cancer is still the leading cause of cancer mortality in women, with an estimated 411 000 annual deaths worldwide, constituting 14% of female cancer deaths[3]. In Europe, breast cancer has been estimated to cause 130 000 deaths annually[7], and in Sweden 1 500 deaths annually[8].

Because of its high incidence and relatively good prognosis, breast cancer is the most prevalent cancer in the world today with an estimated 4.4 million women alive who have had a breast cancer diagnosis within the last 5 years[3]. In Sweden, approximately 28 600 women are alive that have been diagnosed with breast cancer during the last 5 years[4], and about 80 000 with a diagnosis of breast cancer during their life-time.

3.2 DIAGNOSIS

Breast cancer screening using mammography has been recommended by the Swedish National Board of Health and Welfare since 1986 [9]. The current general recommendations are that women aged 40 – 74 should be offered screening mammography every 18 to 24 months[10]. In Sweden, each county council independently decides which age-categories of women are offered mammography. This has given rise to slight variations in the breast cancer screening practise between different county councils. Results from several randomised trials indicate that screening with mammography can reduce mortality from breast cancer with up to 30 %[11]. However, the effectiveness and cost-effectiveness of different screening strategies have been controversial and different studies have reached different conclusions[12-17].
If a suspicious lesion is found by mammography or by clinical examination, a biopsy should be performed. There are several different biopsy techniques available, such as fine-needle aspiration, core needle biopsy, and local surgical biopsy. The goal of a biopsy is to obtain tissue or cells, not only for histological or cytological examination, but also for biological classification in the presence of a malignant tumour.

3.3 TREATMENT

Surgery
Surgery is a cornerstone in the treatment of breast cancer, and for patients with local disease only, surgery can be curative[18]. The surgical approach to a primary breast cancer tumour involves the excision of all invasive cancer with clear margins of excision. Breast conserving surgery (partial mastectomy and lumpectomy) is today the treatment of choice when tumour size allows for radical surgery with a good cosmetic result. This is based on several randomised clinical trials that have demonstrated that survival with breast conserving surgery followed by radiotherapy is equivalent to that with mastectomy[19, 20]. Mastectomy is recommended when contraindications to breast conserving treatment are present. These contraindications include the presence of two or more primary tumours in separate areas of the breast, diffuse malignant-appearing micro-califications, or when there are absolute or relative contraindications to radiotherapy.

Radiotherapy
Radiotherapy following breast conserving surgery is the current standard of care for patients with early breast cancer. The purpose of radiotherapy is to eliminate cancer cells that may remain near the area from where the tumour was removed during surgery. The use of radiotherapy after breast conserving surgery has been shown to reduce the risk for a local recurrence by 60-70% compared to breast conserving surgery alone[20, 21]. Radiotherapy is also indicated when the margins of surgical resection are not clear (or uncertain) of tumour growths, as well as when there is extensive tumour involvement in the axillary lymph nodes. For various reasons, it has been difficult to demonstrate a long-term survival benefit associated with postmastectomy radiotherapy[1]. In the EBCTCG overview of radiotherapy, it was found that the reduction in breast cancer deaths was offset by an increase in non-cancer deaths (mainly from cardiovascular events)[22]. However, this late toxicity is likely to be reduced due to improvements in radiation delivery, which have reduced the treatment fields and the doses to the heart[1, 23, 24].

Adjuvant systematic therapy
The aim of adjuvant systematic therapy is to reduce breast cancer related events (locoregional recurrence; metastatic disease and the occurrence of new primary tumours) as well as to improve survival. This is achieved by eradicating tumour cells that might remain in the body after loco regional treatment (surgery and radiotherapy) has been completed.
Hormonal therapy
Tamoxifen is a Selective Estrogen Receptor Modulator (SERM) which has proven to be highly effective against breast cancer events in patients with hormone receptor-positive breast cancer. For women with hormone receptor-positive breast cancer, five years of adjuvant tamoxifen reduce the annual risk of recurrence by approximately 40% and the annual risk of dying of breast cancer by 35% compared to patients receiving no tamoxifen[25]. These benefits also seem to be persistent, with the difference in fifteen-year probability of death from breast cancer between patients receiving adjuvant tamoxifen compared to patients receiving no tamoxifen being about three times as great as the difference in five-year probability of death from breast cancer[25].

Aromatase inhibitors constitute an alternative to tamoxifen, developed in the 1980s-1990s, to treat postmenopausal women, both with metastatic disease and in the adjuvant setting, with hormone receptor-positive breast cancer. Clinical trials have shown a significant reduction in the risk of breast cancer related events with aromatase inhibitors compared to tamoxifen as either initial treatment[26, 27], or after two-three years of tamoxifen[28, 29] for a total treatment duration of five years. No significant overall survival differences have been noted in these trials. However, a meta-analysis has shown a significant overall survival benefit for patients switching from tamoxifen to aromatase inhibitors after two-three years, compared to continuing with tamoxifen for a total of five years[30].

Chemotherapy
Chemotherapeutic drugs achieve their therapeutic effect by impairing cell division, thereby causing cancer cells (as well as healthy cells) to stop growing and multiplying. An overview analysing the benefits of adjuvant chemotherapy found that six months of anthracycline-based (e.g. doxorubicin, epirubicin) chemotherapy reduces the annual breast cancer death rate by 38% for women younger than 50 years, and by 20% for those aged 50-69 years[25]. The overview also found anthracycline-based chemotherapy to be superior to CMF (cyclophosphamide, methotrexate, fluorouracil) based adjuvant chemotherapy. Studies investigating the addition of a taxane (e.g. docetaxel, paclitaxel) to an anthracycline-based regimen have found evidence of a reduction in recurrence and mortality compared to anthracycline-based chemotherapy alone[1].

Monoclonal antibodies
Trastuzumab is a monoclonal anti-body targeting the extracellular domain of the HER2 protein. Four major adjuvant trials have investigated different adjuvant treatment approaches with trastuzumab[31-35]. These studies have found that one year of adjuvant trastuzumab in addition to adjuvant chemotherapy for women with HER2 positive early breast cancer is associated with a significantly lower risk of recurrence and improved survival compared to adjuvant chemotherapy alone.
Metastatic breast cancer

When the breast cancer has spread from the original site in the breast to other organs or tissues outside the loco regional area in the body, it is referred to as metastatic breast cancer. Metastatic breast cancer is generally considered to be an incurable disease, but treatment can improve survival. Almost all patients with metastatic disease are considered for systematic therapy. The exact choice of therapy depends on the severity of symptoms, hormone-receptor status and HER2 status of the tumour. For patients with hormone receptor-positive tumours, a response to initial hormone therapy is seen in 30 – 50% of these patients[1]. Eventually, most patients with metastatic disease are considered for chemotherapy. The response rates for initial chemotherapy range from 25% to 60%, with a median time to progression of approximately six months[1]. The addition of trastuzumab to chemotherapy for patients with HER positive metastatic breast cancer has been shown to yield a significantly better response rate, time to progression, and survival compared to chemotherapy alone[36, 37].
4 HEALTH ECONOMICS

Health economics can be defined as the application of the theories, tools and concepts of economics as a discipline to the topics of health and health care[38]. Since economics as a science is concerned with the allocation of scarce resources, health economics is concerned with issues relating to the allocation of scarce resources to improve health. This includes resource allocation both between other sectors of the economy and the health care system and to different activities and individuals within the health care system.

Health economics is thus a broad subject and studies in health economics can, among other things, be concerned with economic aspects of health promotion and prevention, the supply and demand of health care, health insurance, regulation of markets for health manpower, costs and benefits of medical research, and economic evaluation of health care. Due to the constant introduction of new treatment alternatives and scarce resources within the health care system, it has become increasingly important to evaluate if new treatment options achieve their health improvements at a reasonable cost. This has led to the emergence of economic evaluation of drugs and other health care interventions as one of the major fields of health economics. An economic evaluation is a key part of a more general health technology assessment (HTA) undertaken to gain information for decisions about new as well as established medical technologies[39].

4.1 ECONOMIC EVALUATION IN HEALTH CARE

Economic evaluation deals with both the input and outcome of an intervention, sometimes referred to as the cost and effects of the intervention. Information about the cost of an intervention is needed in order to perform an economic evaluation. However, the most crucial point when performing economic evaluations of health care is the availability of clear and well documented clinical evidence for the intervention. An economic evaluation is only as good as the underlying effectiveness data, and even the highest quality economic data will not overcome a deficiency in effectiveness data[38]. Therefore, it is seldom worth the effort to make detailed comparisons about costs of interventions, unless at least some relevant data are available about their relative effectiveness.

In the same way, even the best performed study on relative effectiveness cannot by itself determine if the intervention is cost-effective, without making some assumptions about the cost of the alternatives. Economic evaluation also concerns itself with choices. Thus, the most important stage in an economic evaluation is when the alternatives to be compared are defined. An intervention can never be cost-effective by itself, only in relation to a defined alternative for a defined group of patients or indication. Taking these characteristics into consideration, economic evaluation can be defined as the comparative analysis of alternative courses of action in terms of both their costs and consequence[40].
4.2 DIFFERENT TYPES OF ECONOMIC ANALYSIS

The different types of economic evaluations all measure cost in a similar way and are therefore usually distinguished by how the consequences of the compared alternatives are measured. Economic evaluations are usually divided into four categories: cost-minimisation, cost-effectiveness, cost-utility, and cost-benefit analysis [40, 41]. These are summarized in Table 1.

<table>
<thead>
<tr>
<th>Type of evaluation</th>
<th>Outcome measure</th>
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<tbody>
<tr>
<td>Cost-minimisation analysis (CMA)</td>
<td>None, outcomes are assumed to be equal for all alternatives</td>
</tr>
<tr>
<td>Cost-effectiveness analysis (CEA)</td>
<td>One-dimensional clinical outcome (blood pressure, relapse avoided, life-years)</td>
</tr>
<tr>
<td>Cost-utility analysis (CUA)</td>
<td>Multi-dimensional outcome combining survival and quality of life (QALYs)</td>
</tr>
<tr>
<td>Cost-benefit analysis (CBA)</td>
<td>Outcome measured in monetary units</td>
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Cost-minimisation analysis

A cost-minimisation analysis (CMA) can be performed if the alternatives under consideration have identical outcomes, i.e. there are no differences in treatment effectiveness, complication rates etc. In this case, it is enough to compare the costs of the different interventions. In CMA, the decision rule is simple: The least costly alternative should always be chosen since the outcomes are equal. However, since it is rare that two interventions have equal outcomes, the use of CMA is limited.

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is a comparative analysis of both the costs and effects of two or more interventions. The effects are expressed in one-dimensional non-monetary units, either disease specific (blood pressure reduction, relapse avoided etc) or more general, such as life-years gained. When performing CEA, the incremental cost-effectiveness ratio (ICER), as opposed to the average cost-effectiveness ratio, is the relevant variable when deciding on the allocation of resources used to maximise the health effects for a given amount of resources [42]. The incremental cost-effectiveness ratio (ICER) is defined as the ratio of the difference in cost to the difference in effect between the two comparators:

\[
ICER = \frac{\Delta C}{\Delta E} = \frac{C_a - C_b}{E_a - E_b}
\]
Ci represents the cost and Ei represents the effect of intervention i. To properly calculate the ICER for an intervention, that intervention should be compared to the next most effective mutually exclusive, non-dominated, intervention[42]. The ICER can thus be interpreted as the incremental cost of producing effect by one intervention, compared to the next most effective alternative.

In some instances, certain interventions can be dominated by other alternatives[42]. An intervention can be dominated for two reasons. The first reason is usually referred to as “simple dominance”, and arises when an intervention is less effective and more costly compared to an alternative intervention. The second alternative is when an intervention’s ICER is higher than that of the next more effective intervention. This is usually referred to as “extended dominance”. The concept of extended dominance is that the additional effect is produced at a higher marginal cost than necessary.

If disease specific outcome measures (such as blood pressure reduction in mm Hg or myocardial infarction avoided) are used in CEA, the results of the CEA become hard to interpret and a comparison between interventions for other disease areas becomes difficult.

Cost-utility
Cost-utility analysis (CUA) is a special type of CEA that uses a generic multi-dimensional outcome measure including both survival and quality of life. One such outcome measure that is frequently used in CUA is quality adjusted life years (QALY). QALYs are constructed by multiplying the quantity of life years gained by a weight between 0 (Dead) and 1 (Full health) reflecting the quality of that life[41]. This is illustrated in figure 1. However, in order for QALYs to be a valid outcome measure in CUA they must (1) be based on preferences (2) anchored on death and full health and (3) measured on a cardinal scale, meaning that each increment on the scale is of equal value[40].

Figure 1. Quality adjusted life years (QALY)
The main methods for eliciting preferences used to construct QALYs are Standard Gamble (SG), Time-trade Off (TTO) and Rating Scales (RS)[40].

There are several advantages of using QALYs as the unit of effect in economic evaluations. They provide a method for combining all consequences of a treatment into a single multi-dimensional measure. For this reason, CUA can be used to compare interventions between different disease areas and different patient groups. Another advantage is that interventions aimed at improving quality of life can be evaluated against programmes aimed at increasing life. The same dominance rules that apply to CEA also apply to CUA.

Cost-benefit

In cost-benefit analysis (CBA) both costs and consequences are measured in monetary units. Since both costs and benefits are measured in the same monetary unit, interventions with a positive net benefit should be implemented[38]. If there are several competing, mutually exclusive interventions, then the intervention with the highest net benefit should be implemented. In addition, CBA enables a comparison of investments not only within the health care sector but also a comparison of the net benefits of investments in non-health care sectors, such as education and road safety, with those in health care. Benefits are best measured by the maximum willingness to pay (WTP). WTP are subjective valuations of the monetary value of health outcomes, and can be measured by such techniques as contingent valuation questions.

4.3 INTERPRETATION OF COST-EFFECTIVENESS RESULTS

When comparing two different, mutually exclusive interventions with regard to cost and effect, four types of results can emerge. These results can be illustrated in a so-called cost-effectiveness plane (see figure 2). The different interventions are denoted A and B.

If A has a higher effect than B at an equal or lower cost (Q2), then B is said to be dominated by A. If A costs more and has the same or a lower effect (Q4), then A is said to be dominated by B. If A costs more and has a higher effect or costs less and has a lower effect (Q1 and Q3), the ICER must be valued by the decision maker. If the price per effect is used as a decision rule, then the optimal choice will depend on the willingness to pay (WTP) for an additional unit of effect. If the maximum WTP can be defined, intervention A should be preferred to intervention B if the ICER is below this threshold value. In the figure, the maximum WTP is illustrated as the dotted line passing through origo. The maximum WTP is the same for any given gradient, i.e. it is the same all along the dotted line. If the ICER falls below the maximum WTP line (ICER2 and ICER4), then intervention A should be chosen, while if the ICER falls above the maximum WTP line (ICER1 and ICER3), intervention B should be chosen.
4.4 COSTS

A cost can be defined as the value of the resource in its best alternative use of the resource. This is referred to as the opportunity cost. Estimating costs in an economic evaluation involves three steps. First, all relevant resources must be identified, and quantified into physical units, such as outpatient visits or a specific amount of a drug. Second, the physical unit must be valued which means that it is assigned a unit cost. According to economic theory, a resource should be priced based on its opportunity cost. However, in practice, the market price of the resource is often used. Separating the number of units of resources and the valuation of each resource item is important both for the interpretation of the result and for the ensuing opportunities to make sensitivity analysis when, for example, values can vary. The third step is the multiplication of quantities and unit costs.

The costs that should be included in an economic evaluation depend on the perspective of the economic evaluation. Two frequently used perspectives are societal perspective and health care perspective. If a societal perspective is used, then all costs, irrespective of where they arise, should be included in the analysis. If a health care perspective is used, then only costs of health care should be included in the analysis. The Panel on Cost-Effectiveness in Health and Medicine recommends that a societal perspective is used when performing economic evaluations[43].
A distinction is often made between different types of cost. Costs are often separated into direct medical costs, direct non-medical costs, indirect costs, intangible costs and future costs.

Direct medical costs are defined as the resources used within the health care sector. Examples of direct medical costs are working time for doctors and nurses, drugs, equipment, and buildings.

Direct non-medical costs are resources used outside the health care sector in relation to the treatment or as an effect of the treatment. Examples of direct non-medical costs are transport costs to and from the hospital, community services, and informal care by relatives and friends. For informal care, that is a non-market commodity, costing is problematic, and several different costing methods can be applied. If the caregivers are of working age, they may reduce their employment level to care for the patient. In this case, the opportunity cost represents the value of lost production and can be estimated by human capital theory. Informal care can also be associated with a loss of leisure time, which has a value. The loss of leisure time has been suggested to be valued at between zero and average overtime earnings. Another valuation principle is to value informal care at the market price of a close substitute, which is known as the replacement cost method[44].

Indirect costs are defined as resources forgone due to treatment, morbidity, and mortality for those afflicted by the disease. Examples of indirect costs are productivity losses due sick leave, reduced productivity at work, and early retirement caused by a disease. Diseases that mainly affect the elderly who no longer participate in the labour force will thus tend to be associated with low indirect costs.

There are different approaches to the valuation of indirect costs. One approach is to use human capital theory as the basis for valuation[45]. According to human capital theory, the value of production of an individual is considered at market price, in this case the salary of the individual including the employer’s cost of employment. The friction cost method has been suggested as an alternative approach when estimating indirect costs[46]. In a comparison of the two methods, the friction cost method estimated indirect costs to approximately 12% of the indirect costs estimated with human capital theory[46]. However, the friction cost method has been strongly criticised on the grounds that it is based on implausible assumptions not supported by neoclassical economic theory[47].

Intangible costs are consequences that are difficult to measure and for which it is difficult to assign a value. An example is the value associated with reduction or improvements in health. This cost is rarely explicitly included in economic evaluation, but more often incorporated as a utility in the denominator when estimating the ICER.
Future costs are defined as the difference in consumption and production for the years of increased survival with which an intervention is associated. These costs are sometimes called “cost of added years of life”. It has been argued that this difference between consumption and production during life years gained should be included as a cost in economic analysis when using a societal perspective[48, 49]. The size of this cost will be dependent on the age of the individual. Elderly individuals most often consume more than they produce while younger individuals in general produce more than they consume.

4.5 COST OF ILLNESS

A cost of illness study estimates the costs related to a specific disease. This type of study provides important information about the total burden of the disease and where these costs occur in society. However, cost of illness studies should not be considered as economic evaluations, since they do not examine alternatives and their costs and outcomes. Since cost of illness studies do not analyse and compare the improvement in health derived from an intervention with a relevant comparator, they cannot be used for resource allocation decisions aimed at maximising health. No matter how great the cost of a disease, allocating resources to it is futile if there are no effective interventions[38]. However, cost of illness studies can still be policy relevant by educating, informing and enlightening policy-makers[50].

Cost of illness studies are either based on a “bottom-up” or a “top-down” approach[45]. The bottom-up approach estimates the cost per case for a sample of patients with a defined disease, which is then extrapolated to represent the whole population. The difficulty with this approach is to ensure that the sample is unbiased and representative of the overall patient population. The top-down approach means that the total disease related cost for the given perspective is identified, usually using statistical databases and national illness registries. The advantage of using a top-down approach is that no extrapolation is required, thus avoiding the risk of double counting. The disadvantage is that the data needed to estimate the total cost of illness may not be available through statistical databases and national illness registries, thus causing an underestimation of the total cost. Examples of this could be misdiagnosed health care consumption or resource use not assigned to a diagnosis, such as social services.

Cost of illness studies can be performed using either the prevalence or the incidence method[45]. Prevalence based studies examine the cost incurred by a patient population in a given geographical area during a given time period, usually one year, irrespective of the date of onset of the disease. These studies can be useful for health policy makers in planning and budget decisions, since the main components of current spending and lost resources (indirect costs) are identified and can be subjected to saving efforts.
Incident based studies examine the costs for cases of a disease which develop for the first time in that year by estimating lifetime costs for a patient with the disease, from diagnosis to cure or, in chronic disease, to death. Incident based studies can be useful when estimating the impact of a treatment on future burden of disease, including planning for future capacity.

In theory, all relevant costs should be included in a cost of illness study but, in practice, there is a limit to what can be identified and measured. Most cost of illness studies are limited to estimating direct and indirect costs.

4.6 RESOURCE ALLOCATION BASED ON ECONOMIC EVALUATION

How do you decide which intervention to choose, given that the objective is to maximise the effect for the resources spent on interventions? While it is obvious that intervention with an equal or higher effect at a lower cost is preferable to its comparator, this is not necessarily the case for interventions with a higher effect and a higher cost.

Two approaches can be used to decide how resources should be allocated based on economic evaluations. The first approach is to determine the amount of resources (the budget) available to be spent on the different interventions. This is usually referred to as the fixed budget approach. With the budget as the decision rule, the choice of interventions depends on the size of the budget. The intervention with the lowest ICER is implemented first. According to increasing ICER, independent interventions are added, or mutually exclusive treatments are replaced, until the budget is exhausted.

The second approach is to base the decision on the willingness to pay (WTP) for a gained unit of effect (e.g. the value of a gained QALY). When using this approach, an intervention is considered to be cost-effective when the cost per QALY gained is equal to or below a specific cost-effectiveness threshold. Currently, there is no general consensus on the exact cost per QALY gained that defines this cost-effectiveness threshold. Several different methods have been proposed to estimate the value of a QALY, such as Human Capital (HK), Contingent Valuation (CV), and Revealed Preferences (RP). However, these methods produce drastically different results. In a literature overview of the value per QALY estimated in different studies, the median value per QALY based on HK was approximately $25 000 (approximately 225 000 in year 2005 SEK) and the median value per QALY for RP studies based on job risk was approximately $430 000 (approximately 3 896 000 in year 2005 SEK)[51]. In Sweden, the Swedish National Road Administration (Vägverket) uses results from surveys measuring people’s hypothetical willingness to pay for saving a statistical life. What is measured is the amount of money people claim that they would be willing to pay out of their own pocket to reduce their expected (statistical) risk of being killed in a road accident. Based on these surveys, a value per statistical life saved is estimated and then used when considering investment in road safety. The value of a QALY in a Swedish setting can be calculated using statistics on fatal road accidents, life-expectancy, the population utility in different age groups, and the value of a statistical life applied by the Swedish Road Administration.
Using this method, the value of a QALY has been estimated at 655 000 SEK[52]. Another method for inferring a cost-effectiveness threshold value could be based on past reimbursement decisions and guidelines made by national government agencies. Past recommendations by NICE in the UK suggest a threshold value of £20 000 – 30 000 per QALY (approximately 272 000 SEK – 407 000 SEK)[53]. Yet another method could be to base the threshold value on a measure of the country’s economic performance. For example, the WHO Commission on Macroeconomics and Health has suggested that interventions with a cost-effectiveness ratio lower than three times the gross domestic product (GDP) per capita for each averted disability adjusted life year (DALY) could be considered good value for money in developing countries[54]. Using this threshold value for the cost per QALY gained would correspond to a threshold value of approximately 800 000 SEK per QALY gained in a Swedish setting.

Even though there are strong links between the fixed budget approach and the willingness to pay approach, there are some noticeable differences. A fixed budget approach might result in different interventions for different patients within the same patient group at optimum efficiency[42]. This is not the case with the willingness to pay approach, which will always lead to the adoption of the same intervention for all patients in the same patient group.

4.7 MODELLING

Economic evaluations often use data from one or several clinical trials, epidemiological studies, observational studies, and databases with resource use and prices. There is a need for a framework for bringing all these data together, and models can provide such a structure. Models can also be of use when important costs and consequences occur outside the time frame of the clinical studies on which the economic evaluation is based. An example is the survival of patients receiving two different interventions, A and B, during a clinical trial. Intervention A is more effective and patients receiving intervention A live longer. As there are more survivors on intervention A at the end of the trial, limiting the analysis to the trial period would underestimate the difference between the arms even if we assume no treatment effect after the end of the trial. Only analysing the trial period would therefore imply that all additional survivors on intervention A die instantaneously at the end of the trial and that there would be no difference between the interventions beyond this point.

A model can be defined as a simplification of reality, and the goal of model design is to exclude irrelevant details while preserving the important characteristics of the system under study. There are different ways of constructing a model. Three main frameworks can be identified: decision trees, Markov models, and discrete event simulations. However, examples of deviations from the main frameworks are easily found. It should be recognised that the choice of modelling technique is mainly a choice of convenience. As long as all relevant costs and consequences of the different interventions are included, the result should not be dependent on the modelling technique used. The choice of modelling technique should therefore be based on its ability to represent the available data in a simple and transparent way.
**Decision tree models**

A decision tree is a representation of sequential decisions and events with uncertain outcomes. The model structure defines available options for each decision and the possible outcome of each event. By assigning probabilities and values to the different outcomes, the expected value of each outcome can be calculated and the optimal strategy can be identified. Decision tree models are most appropriate for short-term analyses or other situations when the numbers of possible outcomes are limited. An example of a simple decision tree is shown in figure 3.

Figure 3. Decision tree

![Decision Tree Diagram]

**Markov models**

In a Markov model, a simulated cohort of patients is divided into states and time is divided into same length cycles. Each of these states is associated with costs and health effects and the states are mutually exclusive and collectively exhaustive, meaning that patients must be in one (but only one) of the states at any point in time. At the end of each cycle, patients can either remain in the same state, or make a transition to a different health state. Transition probabilities control the flow of patients between states. One important assumption of the Markov model is the no memory assumption, also called the Markovian property, meaning that future events depend only on the current state of the patient, and not on prior events. A Markov model is often illustrated in the form of a state transition diagram, as seen in figure 4.

Figure 4. Markov model

![Markov Model Diagram]
A Markov model is evaluated by moving the simulated cohort of patients through the model, where fractions of the cohort move to different states in each cycle based on the transition probabilities in the model. This generates an estimate of e.g. mean costs and mean survival. The results obtained when running the model using costs, health effects, and transition probabilities associated with different interventions can then be compared, and the incremental costs and effects for the simulated interventions can be calculated.

**Discrete event simulation**

In discrete event simulation, the focus is on events rather than health states. Patients are followed over time and events occur at discrete time points and a list, called the event queue, is maintained to keep track of when the events occur[56]. The triggering of an event may lead to new events occurring later, and they are then added to the event queue in the appropriate order. When an event occurs, the entire system that is being modelled is said to change states. The events are also related to some sort of activity. For example, an activity might be a hospitalisation including a number of events such as hospitalisation, operation, and discharge. The advantage of discrete event simulation is that patients can be involved in several activities at the same time, which would require a separate state for each possible combination of activities in a Markov model.

**4.8 UNCERTAINTY**

Limitations in methods and underlying data will lead to uncertainty in the results of the economic evaluation. The uncertainty in model based cost-effectiveness analyses can be classified into four different categories: methodological uncertainty, modelling uncertainty, transferability/generalisability, and parameter uncertainty[57]. Methodological uncertainty is the uncertainty arising when comparing study results based on different methods, which has been suggested to be handled by sensitivity analysis and agreement upon a reference case model. Modelling uncertainty relates to the structure and processes of the model used in the analysis. This type of uncertainty has been suggested to be handled by sensitivity analysis and letting different groups perform the same analysis. Transferability/generalisability uncertainty arises when the results from the analysis are applied to other settings. Parameter uncertainty is the uncertainty that has been given most attention in model based cost-effectiveness analyses. This uncertainty relates to the limitations of the underlying data used in the model. This type of uncertainty has been suggested to be handled by sensitivity analysis. In sensitivity analysis, uncertain parameters in the analysis are varied to explore the potential consequences on the result. If the conclusion of the analysis remains the same as parameters are varied, the results are deemed robust. However, the selection of parameters and their potential ranges for the sensitivity analysis can be arbitrary and there is no exact definition of when the results can be considered robust[58].

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Another approach when exploring the potential consequences of uncertainty is to undertake probabilistic sensitivity analysis. In probabilistic sensitivity analysis, the uncertainty of underlying parameters is taken into account by allowing some or all of them to vary over a given range with a given distribution. Using these distributions, large sets of values for the underlying parameters are produced. These sets of values generate a distribution of the cost-effectiveness estimate, which can be used to assess the uncertainty. Probabilistic sensitivity analyses can be graphically illustrated as acceptability curves\cite{59, 60}. An acceptability curve shows the proportion of estimates of the ICER that falls below different values of willingness to pay for one unit of health effect. An example of an acceptability curve is shown in figure 5.

Figure 5. Acceptability curve
5 LITERATURE REVIEW

A literature review of the previous research in the area was performed in order to get an overview of the history and development of health economic studies of breast cancer. The review was divided into studies of the cost of breast cancer, utility and quality of life measures using preference based methods, and the cost-effectiveness of breast cancer treatments. Relevant studies were identified using the PubMed database as well as other online sources. Costs are presented both as they appear in the studies as well as inflated to 2005 year prices and converted into Swedish Kronor (SEK) using the average exchange rate for 2005[61] (1 CAD = 6.18 SEK, 1 EUR = 9.28 SEK, 1 GBP = 13.58 SEK, 1 NOK = 1.16 SEK, 1 USD = 7.48 SEK, 1 EUR = 6.56 FRF).

5.1 COST OF BREAST CANCER

The search for literature on the cost of breast cancer resulted in nine studies, presented in table 2. Four studies were from the US, two from Canada, one from France, one from Belgium, and one from the UK. The year of publication ranged from 1996 to 2004.

The study by Rao et al[62] assesses the direct medicare cost of metastatic breast cancer from first diagnosis until death. Patients receiving a diagnosis of metastatic breast cancer between 1 April 1997 and 31 December 1997 were included in the study. A matched case-control study provided a comparison of the costs for cancer and non-cancer patients. A total of 397 patients with metastatic breast cancer were identified and followed for an average of 16.2 months. The mean total direct medical cost was $35 164 (279 000 SEK) per metastatic breast cancer patient and $4 176 (33 000 SEK) per person in the control group.

The study by Remák et al[63] is an incidence based cost of illness study of metastatic breast cancer in the United Kingdom. They estimated the lifetime cost of treatment for female patients in the UK with stage IV disease at first diagnosis of breast cancer to £12 500 (approximately 176 000 SEK) per patient, based on information from a panel of cancer physicians.

Cocquyt et al[64] used a Markov model to estimate the direct cost of breast cancer from diagnosis over a ten-year period. The model used yearly cycles and included 9 different mutually exclusive health states. The cost in each health state was based on a chart review from 118 patients. The total cumulative ten-year cost was estimated to €31 774 (340 000 SEK). Hospital costs represented 30% of the total cost, systemic treatment, surgery and radiotherapy represented 28%, and testing 14%. The first year after node-negative primary breast cancer, node positive primary breast cancer, relapse, and metastatic disease were associated with a cost of €7 717 (82 000 SEK), €14 240 (152 000 SEK), €13 390 (143 000 SEK), and €17 549 (188 000 SEK), respectively.
The study by Warren et al[65] estimated the treatment costs for elderly women (65 and above) with early-stage breast cancer, based on Medicare claims. Women, diagnosed with breast cancer between January 1983 and August 1996, were included in the study. The average long-term cost of health care during from diagnosis to death attributable to breast cancer was estimated to $27,697 (252,000 SEK).

Wai et al[66] estimated health system costs during the interval from diagnosis of first recurrence or metastasis until death for 75 female subjects randomly selected from patients known to have died of breast cancer. The mean total cost for the health system was CAD$36,474 (253,000 SEK) per subject. Inpatient costs accounted for the greatest proportion of the total, over 50% in all age groups.

The study by Will et al[67] estimated the undiscounted life-time cost of breast cancer treatment in Canada to vary between CAD$36,340 (approximately 259,000 SEK) for Stage IV and CAD$23,275 (approximately 166,000 SEK) for Stage I. Inpatient costs were found to constitute a majority of the total life-time costs.

In the study by Bercez et al[68], the costs of different recurrences were evaluated based on the medical records of 146 patients with either distant metastases or a local recurrence followed or not by distant metastases. The estimated cost included both direct medical costs (visits, drugs, treatments, tests, etc) and direct non-medical costs (patient transportation). The annual cost in the year following a local recurrence was approximately 70,000 French Francs (FRF) (111,000 SEK) and the annual cost in the year following a distant metastatic recurrence was approximately 125,000 FRF (199,000 SEK). The total cost was estimated at 115,705 FRF (184,000 SEK) for a local recurrence not followed by metastases. For distant metastatic recurrence, the total cost was 175,168 FRF (279,000 SEK) and the total cost of a local recurrence followed by distant metastases was 287,582 FRF (457,000 SEK).

In the study by Fireman et al[69], the direct medical costs of cancer that occur over the entire course of the disease were estimated. A total of 8,152 patients with breast cancer starting from 1973 were included in the study. The costs were estimated using automated utilization data bases from a Health Maintenance Organisation (HMO), adjusted for the use of medical services not captured by automated data bases based on a chart review of a random sample of 886 patients. From diagnosis until death or 15 years later, the direct cost attributable to breast cancer was estimated to $35,000 (364,000 SEK).
Legorreta et al[70] estimated the cost of breast cancer treatment in a four-year longitudinal study, based on overall medical expenditure in a cohort of patients identified as having breast cancer. They estimated the annual cost to approximately $15,000 (144,000 SEK) in the first year for patients with Stage 0, I, and II breast cancer. For patients with Stage III and IV breast cancer, the annual cost in the first year was approximately $27,000 (259,000 SEK) and $37,000 (355,000 SEK), respectively. In year 2, annual costs decreased for all stages except Stage III. The cost did not differ significantly between stages in years 3 and 4. The cumulative four-year cost for Stage 0, I and II was $18,900 (181,000 SEK), $23,200 (222,000 SEK), and $28,888 (276,000 SEK) respectively. The four-year cumulative cost for Stages III and IV were approximately $60,000 (575,000 SEK), and $50,000 (479,000 SEK) respectively.

The studies reviewed indicate that both local recurrence and distant metastatic recurrence are associated with substantial direct medical costs, with distant metastatic recurrence being the most costly. However, none of the studies examined the indirect costs associated with productivity losses due to breast cancer. Since the studies are conducted in different health care systems at different points in time, a direct comparison of the results is difficult. Another problem which makes direct comparison difficult is that the studies include different cost categories, and use different methodologies and different time-periods for which the costs are measured.
<table>
<thead>
<tr>
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<th>Perspective</th>
<th>Time period</th>
<th>Sample size</th>
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<td>Health care</td>
<td>Lifetime</td>
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<tr>
<td>Remák et al, 2004</td>
<td>UK</td>
<td>Health care</td>
<td>Lifetime</td>
<td>Panel of cancer physicians</td>
</tr>
<tr>
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<td>Belgium</td>
<td>Health care</td>
<td>10 years</td>
<td>118</td>
</tr>
<tr>
<td>Warren et al, 2002</td>
<td>US</td>
<td>Health care</td>
<td>Lifetime</td>
<td>Not stated</td>
</tr>
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<td>Lifetime</td>
<td>75</td>
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<td>Health care</td>
<td>Lifetime</td>
<td>18 300</td>
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<td>France</td>
<td>Health care</td>
<td>10 years</td>
<td>146</td>
</tr>
<tr>
<td>Fireman et al, 1997</td>
<td>US</td>
<td>Health care</td>
<td>Lifetime</td>
<td>8 152</td>
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<tr>
<td>Legorreta et al, 1996</td>
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<td>Health care</td>
<td>4 years</td>
<td>200</td>
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</tbody>
</table>

<table>
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<tr>
<th>Breast cancer state</th>
<th>Type of cost</th>
<th>Cost in 2005 SEK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic breast cancer</td>
<td>Direct</td>
<td>279 000</td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>Direct</td>
<td>176 000</td>
</tr>
<tr>
<td>Node- and node+ primary breast cancer, relapse, metastatic disease</td>
<td>Direct</td>
<td>82 000 – 188 000</td>
</tr>
<tr>
<td>Early breast cancer</td>
<td>Direct</td>
<td>252 000</td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>Direct</td>
<td>253 000</td>
</tr>
<tr>
<td>Stage I, II, III, IV</td>
<td>Direct</td>
<td>166 000 – 259 000</td>
</tr>
<tr>
<td>Local recurrence and/or distant metastatic recurrence</td>
<td>Direct</td>
<td>184 000 – 457 000</td>
</tr>
<tr>
<td>Early breast cancer</td>
<td>Direct</td>
<td>364 000</td>
</tr>
<tr>
<td>Stage 0, I, II, III, IV</td>
<td>Direct</td>
<td>181 000 – 575 000</td>
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</table>
5.2 QUALITY OF LIFE IN BREAST CANCER

In order to use QALYs as a valid outcome measure in economic evaluation, quality weights that represent the health related quality of life (HRQoL) of the health states under consideration are needed[40]. It is important that the QALY weights are based on preferences for the health states. This way, the more desirable (more preferred) health states receive greater weight and will be favoured in the analysis. The main methods for directly eliciting preferences used to construct QALYs are Standard Gamble (SG), Time-trade Off (TTO) and Rating Scales (RS). Preferences for health states can also be measured using generic instruments, such as the EQ-5D which is based on 243 health states that have been ascribed preference weights using the TTO method based on a general population[71], or the Health Utility Index based on the SG method[72].

Our review of the literature showed that several studies have investigated the HRQoL of breast cancer patients using disease-specific instruments that cannot readily be converted into QALY weights[73-85]. However, relatively few studies have investigated the HRQoL of breast cancer patients using preference-based measures.

The study by Conner-Spady et al[86] investigated the HRQoL in 52 breast cancer patients with a poor prognosis, receiving high-dose chemotherapy treatment with autologous blood stem cell transplantation. They reported a mean EQ-5D index value of 0.61 three weeks after completion of the high-dose chemotherapy. Twenty-four months post enrolment into the study, the mean EQ-5D index value had risen to 0.89.

Perez et al[87] assessed the HRQoL of 38 women with metastatic breast cancer during a twelve-month period. The TTO question used in this study was framed in terms of the health status in the preceding month representing the anticipated health status in the month ahead. A booklet containing successively increasing trade-offs in time in order to achieve full health was used. During the twelve-month period, the average amount of days traded ranged between approximately 0.5 and 2, translating into a TTO value of 0.983 to 0.933. It should be noted, however, that the use of a 30 day time-horizon is non-standard for TTO questions.

The study by Jansen et al[88] investigated the HRQoL in 43 patients with early-stage breast cancer undergoing adjuvant chemotherapy. These patients reported a TTO value of 0.93 and a SG value of 0.97 for the actually experienced health state during chemotherapy.

In the study by Hayman et al[89] HRQoL associated with breast cancer was evaluated by 97 breast cancer patients using the SG method. Treatment with conservative surgery and radiation therapy without a local recurrence was found to be associated with a SG value of 0.92. Conservative surgery alone followed by a local recurrence salvaged by conservative surgery and radiation therapy was associated with a SG value of 0.87, and treatment with conservative surgery without radiation therapy, followed by a local recurrence salvaged by mastectomy and reconstructive surgery was associated with a SG value of 0.81.
In the study by Ashby et al[90], a sample of 17 breast cancer patients were asked to evaluate their own situation using the TTO method. These patients had no history of breast cancer recurrence, and considered themselves to be very well. This resulted in a mean TTO value of 0.847. Mean TTO values for five different hypothetical breast cancer scenarios, both by breast cancer patients as well as others, ranged from 0.257 to 0.784. This TTO valuation of hypothetical breast cancer scenarios included responses from breast cancer patients, nurses, hospital doctors, general practitioner, and university staff.

Hall et al[91] used a mixture of 60 breast cancer patients and a community sample of 44 women to evaluate the HRQoL of several hypothetical breast cancer disease scenarios. They reported a TTO value ranging from 0.58 to 0.18 for the scenarios involving breast cancer related death, and TTO values ranging from 0.85 to 0.24 for scenarios related with non-cancer death.

The review showed there to be a large variation in the quality of life weight ascribed to breast cancer. This variation is most likely due to differences in the methodology used to evaluate the health related quality of life, as well as differences between the breast cancer states evaluated. However, the studies seem to indicate that breast cancer is associated with a decrease in health related quality of life.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>County</th>
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<th>Sample size</th>
<th>Breast cancer state</th>
<th>QoL weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conner-Spady et al, 2005</td>
<td>Canada</td>
<td>EQ-5D</td>
<td>52</td>
<td>Stage II and III breast cancer</td>
<td>0.61 – 0.89</td>
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<tr>
<td>Perez et al, 2001</td>
<td>New Zealand</td>
<td>TTO</td>
<td>38</td>
<td>Metastatic breast cancer</td>
<td>0.933 – 0.983</td>
</tr>
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<td>Jansen et al, 2001</td>
<td>Netherlands</td>
<td>TTO &amp; SG</td>
<td>43</td>
<td>Early stage breast cancer</td>
<td>0.93 – 0.97</td>
</tr>
<tr>
<td>Haymn et al, 1997</td>
<td>US</td>
<td>SG</td>
<td>97</td>
<td>Early stage breast cancer</td>
<td>0.81 – 0.92</td>
</tr>
<tr>
<td>Ashby et al, 1994</td>
<td>UK</td>
<td>TTO</td>
<td>17</td>
<td>Early stage breast cancer</td>
<td>0.85</td>
</tr>
<tr>
<td>Hall et al, 1992</td>
<td>Australia</td>
<td>TTO</td>
<td>60 + 44</td>
<td>Hypothetical scenarios</td>
<td>0.18 – 0.58</td>
</tr>
</tbody>
</table>
5.3 COST-EFFECTIVENESS OF BREAST CANCER TREATMENTS

The review of cost-effectiveness studies was restricted to published cost-effectiveness studies of pharmaceutical therapies. In total, 29 cost-effectiveness studies of different breast cancer treatments were identified. The studies were categorised into four types of treatment: chemotherapy (6), hormone therapy (14), monoclonal antibodies (7), and bisphosphonates (2).

Two studies evaluated chemotherapy as an adjuvant treatment[92, 93]. Both studies focused on women with node-positive breast cancer, and both studies found their respective intervention to be cost-effective. Four studies evaluated chemotherapy for advanced or metastatic breast cancer[94-97]. The study by Li et al[94] found vinorelbine + mitomycin to be a cost-effective option as a second-line treatment for metastatic breast cancer when compared to paclitaxel, docetaxel and mitomycin + vinblastine. Leung et al[95] evaluated the cost-effectiveness of paclitaxel, docetaxel, and vinorelbine for women with anthracycline-resistant metastatic breast cancer, and found that vinorelbine was associated with lower costs and longer quality-adjusted progression-free survival than both docetaxel and paclitaxel. However, it should be noted that the higher utility values assigned to vinorelbine treatment in the analysis had a large impact on the results, since docetaxel was stated to have both the highest response rate and the longest time to progression, while vinorelbine was stated to have the lowest response rate and the shortest time to progression. The study by Brown et al[96] found that docetaxel increased the cost per patient and yielded higher health benefits compared to paclitaxel for patients with metastatic breast cancer, and that the additional health benefits were achieved at a reasonable cost. Launois et al[97] evaluated the cost-effectiveness of paclitaxel, docetaxel, and vinorelbine as second-line treatment for metastatic breast cancer and found docetaxel to dominate the other alternatives. Although this result is consistent with the findings of Brown et al, it is quite different from the conclusions of Li et al and Leung et al. The difference is most likely due to the different clinical studies used to estimate health benefits derived from the different treatments and the utility weights associated with the different treatments.

Several studies have evaluated the cost-effectiveness of hormone treatment for breast cancer, both in the adjuvant setting and in the advanced and metastatic setting[98-111]. The results of these studies are reasonably consistent, with all of the studies showing that aromatase inhibitors are cost-effective treatment options compared to tamoxifen or megestrol for early as well as advanced / metastatic breast cancer. Although there are no head-to-head clinical trials comparing different aromatase inhibitors, some attempts have been made to indirectly compare the cost-effectiveness of the different aromatase inhibitors. The two studies by Skedgel et al[108, 109] found that adjuvant tamoxifen for 2.5 years followed by exemestane for 2.5 years was the preferred aromatase inhibitor strategy compared to adjuvant anastrozole for 5 years and 5 years of tamoxifen followed by letrozole for 3 years (the Letrozole strategy was only evaluated in one of the studies by Skedgel et al).
The two studies by Marchetti et al[110] and Dranitsaris et al[111] have both compared anastrazole and letrozole for advanced / metastatic breast cancer. These studies found that both anastrazole and letrozole were cost-effective alternatives compared to tamoxifen. However, the study by Dranitsaris et al concluded that letrozole had a better cost-effectiveness ratio than anastrazole, while Marchetti et al found that anastrazole had a better cost-effectiveness ratio compared to letrozole.

Trastuzumab is monoclonal antibody that can be used for the treatment of breast cancer. Three separate studies evaluating the cost effectiveness of trastuzumab for metastatic breast cancer were found in our review[112-114]. The study by Hornberger et al[112] found that trastuzumab + chemotherapy was cost effective for patients with HER2 positive metastatic breast cancer. However, two subsequent studies by Elkin et al[113] and Norum et al[114] estimated the incremental cost-effectiveness ratio to be higher than what is normally considered cost-effective. The reason for the difference in results between these studies seems to mainly be due to how the cross-over from chemotherapy alone to trastuzumab was handled in the analysis. Hornberger et al had access to clinical trial data and could thus estimate the difference in effect between patients receiving trastuzumab + chemotherapy and patients receiving chemotherapy alone (no cross-over). Elkin et al did not have access to trial data, and instead tried to adjust for the cross-over effect in the analysis. However, it is difficult to judge the impact of this adjustment on the final results. The study by Norum et al did not take the cross-over effect into consideration, making it very likely that they have overestimated the cost per QALY gained from trastuzumab + chemotherapy in their analysis.

To our knowledge, there are four studies available that evaluate the cost-effectiveness of adjuvant trastuzumab[115-118]. All these studies have consistent results, reaching the conclusion that adjuvant trastuzumab is a cost-effective treatment option for women with HER2 positive early breast cancer who have completed adjuvant chemotherapy.

Our review also found two studies that evaluated the cost-effectiveness of bisphosphonates as a treatment for patients with metastatic disease and bone metastases. The study by Botteman et al[119] found bisphosphonates to be either cost-saving or having a low cost per QALY gained compared to no treatment. The study by De Cock et al[120] found oral ibandronate to be less costly and have a slight gain in QALY compared to intravenous zoledronic acid and intravenous pamidronate.
To conclude, it can be said that there is a substantial body of literature concerned with the economic evaluation of breast cancer treatments. The most common countries of study were the US and the UK, with 6 studies each. A total of 16 studies were for European countries, while 10 of the studies were for North America. The most commonly used outcome measure was quality adjusted life years (QALY) gained, which was used in 18 studies. Life years (LY) gained were used in 7 studies, and quality adjusted progression free years (QAPFY) gained were used in 4 of the studies. Almost all the studies only included direct costs in their analysis. Although this is in part due to some of the studies being based on patients that were no longer of working age, it nevertheless seems to indicate a lack of data concerning the indirect costs associated with breast cancer. The omission of indirect costs could bias the results of some of these studies, in particular studies evaluating therapy for younger patients.
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</table>

FEC = fluorouracil, epirubicin, cyclophosphamide; VM = vinorelbine, mitomycin; MV = mitomycin, vinblastine; QAPFY = quality-adjusted progression-free year; CMF = cyclophosphamide, methotrexate, fluorouracil; BC = breast cancer; MBC = metastatic breast cancer; EBC = early breast cancer; HR+ = hormone receptor-positive;

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6 MATERIALS AND METHODS

6.1 COST OF ILLNESS OF BREAST CANCER IN SWEDEN (PAPER I)

6.1.1 Costing method

We used a top-down, prevalence based approach when estimating the cost of illness of breast cancer in Sweden. A societal perspective was used, with the inclusion of the following cost categories: screening costs, inpatient care costs, outpatient care costs, drug costs, and indirect costs due to productivity losses (sick-leave, early retirement, and premature death). The human capital approach was used when estimating the indirect costs[45].

6.1.2 Materials

In this top-down study, we used both aggregated and individual resource data from various sources to calculate the cost of illness of breast cancer. Data on screening attendance, age group screened, and screening interval were gathered from the study by Duffy et al[121]. Together with data on the Swedish population[122], this was used to estimate the number of females screened for breast cancer. Individual patient data on hospital inpatient care for breast cancer patients were delivered from the Swedish National Board of Health and Welfare. This registry covers all inpatient hospital care for Sweden. The number of hospital outpatient consultations and general practitioner consultations with the diagnosis breast cancer was gathered from Medical Index Sweden[123]. An estimate of the number of drug prescriptions with breast cancer as the main reason/diagnosis was also gathered from Medical Index Sweden. The indirect costs of sick-leave due to breast cancer were estimated based on data on total expenditure for sick-leave distributed on diagnosis available from the Swedish National Social Insurance Board[124]. Data on the number of female patients in early retirement due to all types of tumours were gathered from the literature[125]. To estimate the number of females in early retirement due to breast cancer, the average of the ratio of female breast cancer incidence to total female cancer incidence[126] in ages 40 – 64 and the ratio of female deaths from breast cancer to female deaths from all cancers[127] ages 45 – 64 was used as a proxy. Data on the age at death and the cause of death for patients with breast cancer were delivered by the National Board of Health and Welfare, making it possible to estimate the number of working years lost due to breast cancer.
6.2 COST AND QUALITY OF LIFE IN DIFFERENT STATES OF BREAST CANCER (PAPERS II-III)

6.2.1 Study design and data collection procedure

The aim was to collect information about costs and health related quality of life in different states of breast cancer in Sweden. The study was designed as a naturalistic cross-sectional observational study. Patients were recruited as they attended a breast cancer outpatient clinic (Radiumhemmet) at the Department of Oncology at Karolinska University Hospital, Solna, Sweden. This is the main outpatient clinic in Stockholm County, which comprises 1.9 million inhabitants. Female patients with a previous diagnosis of breast cancer were eligible for inclusion. The study protocol was approved by the local ethical committee, and informed consent was obtained from all patients prior to inclusion. Patients who fulfilled the inclusion criteria were enrolled consecutively, provided that they agreed to participate in the study. A self-administered questionnaire was distributed to the study sample by a research nurse while patients were waiting to see the doctor / nurse. The questionnaire gathered data on demographic variables, informal care provided by family and friends, work capacity, and health related quality of life. The study did not alter or influence the treatment received by the patients in any way, and the choice of treatment method was entirely controlled by the attending physician. Patients were only included once in the study, even if they repeatedly attended the outpatient clinic during the recruitment period. The breast cancer disease state was determined based on epidemiological data from the Stockholm Oncology Centre (OC). The data included the date of diagnosis and ICD-10 codes for all primary breast cancer, occurrence of contra-lateral breast cancer, loco-regional recurrence, and distant recurrence for patients in the OC database.

6.2.2 Patient sample

The initial patient sample consisted of 361 patients, but was subsequently reduced to 345 patients due to lack of epidemiological data on 16 patients. The patient age ranged from 28 to 93 and the mean age was 57 when included in the study. 78% of the patients were aged below 65, and 52% of the patients were aged between 50 and 65. The majority of the patients were married or co-habiting, and had a higher education in addition to compulsory education. The year of primary diagnosis ranged from 1966 to 2005, with a majority of the patients having been diagnosed with primary breast cancer in 2001 or later. Of the patients responding to the questionnaire, 21% were in their first year after primary breast cancer, 6% were in their first year after a recurrence, 54% had not had a primary breast cancer or recurrence for at least one year, and 19% had metastatic disease.
6.2.3 Resource use

Data on resource use was collected using both register sources and self-administered questionnaires. Medical resource use was collected retrospectively for each patient included in the study from electronic records available through Karolinska University Hospital. The electronic record contained all inpatient admissions and outpatient visits to all hospitals in Stockholm County. In order to calculate the resource use associated with current breast cancer treatment strategies, only admissions and visits starting in 2004 were included in the analysis. The use of outpatient drugs was estimated based on expert opinion. Informal care and productivity losses due to breast cancer (such as absence from work and early retirement) were based on questionnaire answers provided by the patients in the study sample.

6.2.4 Costing

The basic costing principle of collecting data on resource use and multiplying each resource (quantity) with a unit cost (price) was used. In the electronic records available through Karolinska University Hospital, each inpatient admission and outpatient visit was assigned a specific unit cost. These unit costs were used when estimating the inpatient care and outpatient care cost. Unit costs for drugs were derived from the Swedish pharmaceutical reference book (www.fass.se). The cost per hour of informal care is more difficult to estimate, since it can be considered as a non-market commodity and therefore, no market price is available. We assumed the opportunity cost of giving informal care to be a loss of leisure time for the caregiver. To estimate the cost of leisure time lost, we used 35% of the gross wage rate as a proxy[41]. The indirect costs were based on human capital theory[45]. The valuation of lost production due to absence from work (e.g. sick-leave) was based on the hourly pre-tax salary[128], adjusted to the 2005 year level[129], including social insurance contributions paid by the employer[130]. To estimate the value of production foregone from early retirement due to breast cancer, annual income from employment and business[131] including social insurance contributions[130] was used. The underlying rational was that if patients had not had breast cancer, early retirement due to breast cancer would not arise and thus, the patients would have an annual income comparable with the national average for the same sex and age group.

6.2.5 Health related quality of life

The health related quality of life (HRQoL) was measured for each of the patients in the study sample using a direct TTO question and the EQ-5D self classifier.

The direct TTO question was phrased in the following manner: “Imagine the following situation. You are told that you have 10 years left to live, and at the same time you get the choice between living these 10 years in your current health state, OR give up one / some years in order to live in full health. Full health in this case should be the best state imaginable, both physically and mentally, free from all diseases and pain”.

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The patients were then asked to mark on a horizontal graded scale from 0 – 10 years the number of years in full health that they though were equal to living 10 years in their current health state. The TTO score was calculated by dividing by 10 the number of years in full health that the patients judged as equal to living 10 years in their current health state[40].

The EQ-5D self classifier is a validated, standardised, non-disease-specific instrument for describing and valuing health states[40, 71, 132, 133]. The EQ-5D contains five dimensions, each with three levels of severity. The five dimensions are: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Severity is stated as: no problems, moderate problems, or severe problems. The five dimensions with three levels of severity divide health status into 243 (3^5) possible health states. Social tariff values for each of these health states, based on TTO values from the general population, have been estimated by Dolan et al[71]. Their model can generate negative values for certain health states. In our analysis, these negative values were set to zero.

6.2.6 Statistical analysis

The Shapiro-Wilk’s test was used to test the normality of both the cost data and the HRQoL data[134]. We found the cost data as well as the HRQoL data to be non-normally distributed. Due to the non-normal distribution, a two-sample Wilcoxon rank-sum (Mann-Whitney) test was used. The Wilcoxon rank-sum test is a nonparametric alternative to the two-sample t-test, and it is based on the order in which the observations from the two samples fall[135]. It was used to test for differences in resource use and costs between two disease states. This test was also employed to test for differences in HRQoL values between disease states as well as differences between EQ-5D index values and TTO values for matching disease states. A Kruskal-Wallis test is a non-parametric rank analogue of one-way analysis of variance[135]. This was used to test for differences in costs, EQ-5D index value and TTO value between the different disease states. To illustrate the uncertainty in the average point scores given for costs and HRQoL values, 95% confidence intervals of the mean have been estimated using bias-corrected and accelerated bootstrapping with replacement[136]. The number of replications were 1 000. All calculations were made using Stata 8.0 for Windows.
6.3 MODELLING THE COST-EFFECTIVENESS OF BREAST CANCER TREATMENTS (PAPERS IV-V)

Trastuzumab (Herceptin®, Roche) is a humanized monoclonal antibody that has been shown to increase the time to progression and overall survival in patients with HER2-positive metastatic breast cancer, when given as either monotherapy[137, 138] or in combination with chemotherapy[36, 37]. The drug has also, based on large randomized trials, been shown to reduce the risk of recurrence in women with HER-2-positive early breast cancer when given as adjuvant treatment[31-35]. To estimate the cost-effectiveness of trastuzumab, a model is needed which can combine clinical, epidemiological, economic, and health related quality of life data. Two studies were conducted to estimate the cost-effectiveness of trastuzumab in Sweden; one based on patients with metastatic breast cancer receiving trastuzumab and one based on patients with early breast cancer receiving adjuvant trastuzumab.

6.3.1 Modelling approach

Two separate Markov simulation models were developed, one to simulate metastatic breast cancer patients receiving trastuzumab and one to simulate patients with early breast cancer receiving adjuvant trastuzumab. Both models were created using DATA Pro (TreeAge, Williamstown, MA).

Metastatic model

This model was developed to evaluate the cost-effectiveness of several different HER2 testing and trastuzumab + chemotherapy strategies compared to chemotherapy alone for patients with metastatic breast cancer, based on a societal perspective in a Swedish setting.

The model is divided into three different states: “Stable metastatic disease”, “Progressive metastatic disease”, and “Dead”. Patients start in the state “Stable metastatic disease” and are then moved through the states of the model in monthly cycles according to a set of transition probabilities. Patients can either remain in “Stable metastatic disease” or make a transition to the state “Progressive metastatic disease” or the absorbing state “Dead”. Patients in “Progressive metastatic disease” can either remain in that state, or make a transition to “Dead”. Cost and utilities were assigned for each state in the model. The reference patient was a 65 year old female with metastatic breast cancer. The model is depicted in figure 6.
Adjuvant model
The purpose of the adjuvant model was to evaluate the cost-effectiveness of several different HER2 testing and adjuvant trastuzumab strategies compared to no additional adjuvant treatment for patients with early breast cancer that had been given adjuvant chemotherapy, using a societal perspective in a Swedish setting. The model consists of five different states: “No recurrence”, “Loco-regional recurrence”, “Contra-lateral recurrence”, “Distant recurrence” and “Dead”.

The model uses yearly cycles and the flow of patients between the different states is controlled by a set of transition probabilities. All patients start in the state “No recurrence” where they either receive one year of adjuvant trastuzumab treatment after adjuvant chemotherapy or no additional adjuvant therapy (standard care) after adjuvant chemotherapy. In the state “No recurrence”, patients can transition to any of the other states, or remain in “No recurrence”. Patients in the state “Loco-regional recurrence” can remain in that state, or make a transition to “Distant recurrence” or “Dead”. Similarly, patients in the state “Contra-lateral recurrence” can remain in that state, or make a transition to “Distant recurrence” or “Dead”.

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In the state “Distant recurrence”, patients can either make a transition to “Dead”, or remain in that state. Cost and utilities were assigned for each state in the model. However, it should be noted that the first year in either “Loco-regional recurrence” or “Contra-lateral recurrence” is associated with a different cost and utility compared to the second and following years in either “Loco-regional recurrence” or “Contra-lateral recurrence”, due to the additional treatment patients undergo in the first year following a recurrence. The reference patient was a 55 year old woman with early breast cancer that had been completely excised and treated with at least four cycles of adjuvant chemotherapy. The model is depicted in figure 7.

6.3.2 Data

To evaluate the cost-effectiveness of treatments for breast cancer using a modelling approach, three different types of data need to be combined: clinical data (e.g. effect of treatment), epidemiological data (e.g. risk of recurrence and mortality), and health economic data (e.g. costs and health related quality of life).

Clinical data

The base case analysis of the metastatic model was based on the randomised trial by Marty et al[37]. In this study, it was possible for the patients to crossover from receiving chemotherapy alone to receiving trastuzumab plus chemotherapy after disease progression. Since our goal was to compare trastuzumab plus chemotherapy with chemotherapy alone, and not trastuzumab plus chemotherapy with chemotherapy alone plus possible crossover to trastuzumab, we used the overall survival of patients that had not crossed over. The median time to progression and overall survival for patients receiving trastuzumab plus chemotherapy and patients receiving chemotherapy alone (no crossover) were used to estimate the transition probabilities between the different states of the metastatic model.

The clinical effect data used in the adjuvant model were based on the HERA trial[31, 34]. The HERA trial found the hazard ratio of an event (such as the development of a contra-lateral breast or the recurrence of breast cancer at any site) to be 0.64 for patients treated with one year of adjuvant trastuzumab after adjuvant chemotherapy compared to patients that had no adjuvant trastuzumab after adjuvant chemotherapy. This risk reduction was applied to the risk of loco-regional recurrence, contra-lateral recurrence, and distant recurrence for HER2 positive patients in the “No recurrence” state receiving one year of adjuvant trastuzumab.
Epidemiological data
In the metastatic model, time to progression and overall survival for Swedish metastatic breast cancer patients were based on the clinical study by Marty et al.[37]. In the adjuvant model, we used a sample of 20,624 patients from the Stockholm Oncology Centre database to calculate the risk of recurrence and mortality for Swedish breast cancer patients. Weibull regression models, with age as a covariate, were used to estimate the risk of loco-regional recurrence, contra-lateral cancer and distant recurrence as well as the mortality following any of these types of recurrence. Weibull models were chosen because they are suitable for modelling data with either increasing or decreasing hazard rates over time[139]. Other cause mortality (i.e. mortality caused by anything except breast cancer) was included in both the metastatic model and the adjuvant model. The other cause mortality was estimated based on mortality rates for the general female population in Sweden[140], the total number of deaths due to breast cancer in Sweden[8], and Swedish population figures in different age groups[141].

Health economic data
Both economic evaluations used a societal perspective. Based on the findings in Paper II, the costs included in these studies were: inpatient care costs, outpatient care costs, drug costs, informal care, and indirect cost. Drug costs not estimated in Paper II, such as the drug cost for the specific interventions of trastuzumab evaluated in the studies, were derived from the Swedish pharmaceutical reference book (www.fass.se). The costs of cardiac related adverse events related to trastuzumab treatment were based on the DRG cost for heart failure and shock (DRG 127)[142]. The cost for cardiac monitoring and diagnostics tests used to determine HER2 status was gathered from an official price list of a large university hospital[143]. Future costs were based on estimates by Ekman et al[144].

Health related quality of life measurements from Paper III were used in both the metastatic and adjuvant model to estimate the total amount of quality adjusted life-years associated with the different treatments strategies being evaluated. In the metastatic model, the average EQ-5D index value reported by patients with metastatic breast cancer was used as a QALY weight. In the adjuvant model, QALY weights were based on Swedish population health related quality of life data[145], adjusted for the percentage decline in health related quality of life for each breast cancer disease state compared with the general age- and sex-matched population. All costs and effects were discounted at 3%.
7 RESULTS
7.1 COST OF ILLNESS OF BREAST CANCER

The total economic cost of breast cancer in Sweden in 2002 was estimated to approximately 3 billion SEK using a top-down prevalence based approach. Indirect costs, amounting to 2.1 billion SEK, constituted a majority of the total costs. Production losses due to mortality were the main cost component of indirect costs, while hospitalisations and hospital outpatient care were the main cost components of direct costs. Table 5 summarises the calculations and results of the cost of illness estimate for Sweden in 2002.

Table 5. Cost of breast cancer illness

<table>
<thead>
<tr>
<th>Resource</th>
<th>Unit type/cost item</th>
<th>Quantity</th>
<th>Price or cost per unit</th>
<th>Cost in SEK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td>Women screened</td>
<td>665 751</td>
<td>300</td>
<td>199 700 000</td>
</tr>
<tr>
<td>Inpatient care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients alive 2002</td>
<td>Hospitalisation episodes</td>
<td>9 468</td>
<td>+</td>
<td>279 300 000</td>
</tr>
<tr>
<td>patients that died 2002</td>
<td>Hospitalisation episodes</td>
<td>1 652</td>
<td>+</td>
<td>46 100 000</td>
</tr>
<tr>
<td>Outpatient care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital outpatient</td>
<td>Consultations</td>
<td>95 450</td>
<td>2 850</td>
<td>272 000 000</td>
</tr>
<tr>
<td>general practitioner</td>
<td>Consultations</td>
<td>19 550</td>
<td>742</td>
<td>14 500 000</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATC group N02</td>
<td>Prescriptions</td>
<td>11 000</td>
<td>566</td>
<td>6 200 000</td>
</tr>
<tr>
<td>ATC group L01</td>
<td>Prescriptions</td>
<td>1 000</td>
<td>3 735</td>
<td>3 700 000</td>
</tr>
<tr>
<td>ATC group A04</td>
<td>Prescriptions</td>
<td>8 000</td>
<td>2 254</td>
<td>18 000 000</td>
</tr>
<tr>
<td>Remaining</td>
<td>Prescriptions</td>
<td>54 000</td>
<td>1 020</td>
<td>55 100 000</td>
</tr>
<tr>
<td><strong>Total direct cost</strong></td>
<td></td>
<td></td>
<td></td>
<td>894 800 000</td>
</tr>
<tr>
<td><strong>Indirect costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick-leave</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial two weeks</td>
<td>Working weeks lost</td>
<td>8 655</td>
<td>5 633</td>
<td>48 800 000</td>
</tr>
<tr>
<td>Following weeks++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early retirement</td>
<td>Working years lost</td>
<td>1 300</td>
<td>292 900</td>
<td>380 600 000</td>
</tr>
<tr>
<td>Mortality</td>
<td>Working years lost</td>
<td>3 770</td>
<td>292 900</td>
<td>1 104 200 000</td>
</tr>
<tr>
<td><strong>Total indirect cost</strong></td>
<td></td>
<td></td>
<td></td>
<td>2 105 300 000</td>
</tr>
<tr>
<td><strong>Total cost of breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td>3 000 100 000</td>
</tr>
</tbody>
</table>

† Unit cost depended on DRG code of hospital episode

++ Following weeks = \((\text{Total expenditure on sick-leave due to breast cancer} / \text{percentage of income reimbursed by the Swedish National Social Insurance Board}) \times \text{labour cost/wage ratio}\)

+++ Following weeks = \((318 163 232 / 0.8) \times 1.4375 = 571 700 000\)
7.2 COST IN DIFFERENT STATES OF BREAST CANCER

Patients were divided into mutually exclusive and collectively exhaustive disease states based on epidemiological data concerning their breast cancer. The disease states were constructed to represent states that were relevant both clinically as well as for decision modelling. These states were: first year after primary breast cancer (State P), first year after recurrence (State R), second and following years after primary breast cancer / recurrence (State S), metastatic disease (State M). Costs for inpatient care and outpatient care, drugs in outpatient care, informal care, and indirect costs arising from absences from work and early retirement due to breast cancer are presented in figure 8, stratified on age and disease state.

Figure 8. Annual costs for different ages and disease states

Indirect costs constituted the largest cost for patients aged less than 65, with costs of inpatient and outpatient care being the second largest cost for these patients. For patients aged 65 years and over, inpatient and outpatient costs constituted the largest cost. The total cost was substantially higher for patients in State P, State R, and State M compared to State S.
7.3 HEALTH RELATED QUALITY OF LIFE IN DIFFERENT STATES OF BREAST CANCER

The health related quality of life in different breast cancer disease states was assessed using both the EQ-5D questionnaire and a direct TTO question. Patients in their first year after primary breast cancer (State P) reported a substantially lower EQ-5D index value compared to an age and sex match Swedish population. This reduction in HRQoL was mainly due to pain and discomfort as well as anxiety and depression. Patients in their first year after recurrence (State R) reported a higher EQ-5D index value than patients in State P, the difference between these states being due to a smaller proportion of patients reporting problems with pain and discomfort in State R. Patients in their second and following years after primary breast cancer / recurrence (State S) reported an EQ-5D index value similar to State R, but reported a higher TTO value. Patients with metastatic disease (State M) reported the lowest EQ-5D index value as well as the lowest TTO value. Just as for State P, the main driver behind this reduction in HRQoL in State M was due to pain and discomfort as well as anxiety and depression. Our results also showed that all states reported lower EQ-5D index values than TTO values, and that all states reported lower TTO values and lower EQ-5D values compared to an age and sex match Swedish population. The results are presented in figure 9.

Figure 9. Utility in different disease states

![Utility in different disease states](image-url)
7.4 COST-EFFECTIVENESS OF TRASTUZUMAB IN METASTATIC BREAST CANCER

Using the metastatic Markov model described in section 3.3.1, the cost-effectiveness of five different HER2 testing and trastuzumab treatment strategies was evaluated. The result of the base case analysis is given in Table 6. Strategy 1 was the least costly and least effective treatment option. Strategies 2 and 3 were dominated. Strategy 4 had an ICER of 485 000 SEK and Strategy 5 had an ICER of 561 000 SEK, which is normally considered cost-effective.

Table 6. Cost-effectiveness of trastuzumab for metastatic breast cancer

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (SEK)</th>
<th>∆ Cost (SEK)</th>
<th>Effect (QALY)</th>
<th>∆ Effect (QALY)</th>
<th>ICER (SEK/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CH for all patients</td>
<td>331 668</td>
<td>-</td>
<td>1.280</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. T for IHC 3+ patients CH all other patients</td>
<td>395 398</td>
<td>-</td>
<td>1.408</td>
<td>-</td>
<td>Dom++</td>
</tr>
<tr>
<td>3. T for IHC 2+ and 3+ patients CH all other patients</td>
<td>438 429</td>
<td>-</td>
<td>1.456</td>
<td>-</td>
<td>Dom+</td>
</tr>
<tr>
<td>4. T for IHC 2+ and 3+ confirmed to be FISH+ CH all other patients</td>
<td>416 732</td>
<td>85 064</td>
<td>1.456</td>
<td>0.175</td>
<td>485 000</td>
</tr>
<tr>
<td>5. T for FISH positive patients CH all other patients</td>
<td>425 174</td>
<td>8 442</td>
<td>1.471</td>
<td>0.015</td>
<td>561 000</td>
</tr>
</tbody>
</table>

++ Dominated by simple dominance
Dom++ Dominated by extended dominance

CH = chemotherapy, T = trastuzumab and chemotherapy, IHC = immunohistochemical test, FISH = fluorescence in situ hybridization test

Our sensitivity analysis showed that the utility scores used for patients with metastatic breast cancer in the model had a substantial impact on the result, with the utility scores being inversely correlated with the cost per QALY gained. Using the TTO values from Paper III, which are higher than the EQ-5D index values used in the base case analysis, would thus give an ICER of 405 000 for strategy 4 and 469 000 for strategy 5. Using life-years gained as a unit of effect instead of QALYs would further reduce the ICER to 332 000 for Strategy 4 and 384 000 for Strategy 5.
7.5 COST-EFFECTIVENESS OF ADJUVANT TRASTUZUMAB

To estimate the cost-effectiveness of one year of adjuvant trastuzumab after adjuvant chemotherapy, the adjuvant Markov model described in section 3.3.1 was used. The risk of breast cancer recurrence and mortality was estimated from a large (n=20,624) sample of Swedish breast cancer patients. The benefit of one year of adjuvant trastuzumab after adjuvant chemotherapy compared to adjuvant chemotherapy alone was based on the HERA trial, and included in the model as a reduced risk of breast cancer recurrence for patients receiving one year of adjuvant trastuzumab. In total, five different HER2 testing and adjuvant trastuzumab treatment strategies were evaluated. The result is presented in Table 7.

Table 7. Base case cost-effectiveness analysis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (SEK)</th>
<th>∆ Cost (SEK)</th>
<th>Effect (QALY)</th>
<th>∆ Effect (QALY)</th>
<th>ICER (SEK / QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ACH for all patients</td>
<td>1 068 858</td>
<td>11.020</td>
<td>11.020</td>
<td>11.020</td>
<td>11.020</td>
</tr>
<tr>
<td>2. AT for IHC 3+ patients CH all other patients</td>
<td>1 136 609</td>
<td>- 11.211</td>
<td>- 11.211</td>
<td>- Dom++</td>
<td></td>
</tr>
<tr>
<td>3. AT for IHC 2+ and 3+ patients CH all other patients</td>
<td>1 199 152</td>
<td>- 11.281</td>
<td>- 11.281</td>
<td>- Dom+</td>
<td></td>
</tr>
<tr>
<td>4. AT for IHC 2+ and 3+ confirmed to be FISH+ ACH all other patients</td>
<td>1 156 296</td>
<td>87 437</td>
<td>11.282</td>
<td>0.262</td>
<td>333 931</td>
</tr>
<tr>
<td>5. AT for FISH positive patients ACH all other patients</td>
<td>1 164 942</td>
<td>8 646</td>
<td>11.304</td>
<td>0.022</td>
<td>384 946</td>
</tr>
</tbody>
</table>

+ Dominated by simple dominance
++ Dominated by extended dominance

ACH= adjuvant chemotherapy alone, AT = one year of adjuvant trastuzumab after adjuvant chemotherapy, IHC = immunohistochemical test, FISH = fluorescence in situ hybridization test

The risk reduction of breast cancer recurrence was found to be the most sensitive parameter, with 30% changes in this parameter causing the ICER to exceed what is normally considered cost-effective. Duration of the treatment effect and the inclusion of future costs also had a noticeable influence on the result. Assuming that patients had no new breast cancer recurrences 10 years after their primary breast cancer increased the ICER of Strategy 4 and Strategy 5, but did not cause it to exceed what is normally considered cost-effective. Subgroup analysis based on the age of patients at the start of adjuvant trastuzumab treatment showed that the cost per QALY gained was related to age, with younger patients having a lower cost per QALY gained.
8 DISCUSSION

8.1 THE COST OF BREAST CANCER IN SWEDEN

Breast cancer causes a substantial economic burden to both the health care system and society. The study found that the main part of the total cost of approximately 3 billion SEK in 2002 was indirect costs arising from production losses caused by morbidity and mortality due to breast cancer. Hospitalisation was found to be the main cost-driver behind the direct costs, with outpatient care being the second largest cost-driver of direct costs. The high indirect costs indicate that a substantial amount of the life years lost from breast cancer occurs among women who are working when contracting the disease. In table 8, the cost of breast cancer is compared to other illnesses.

Table 8. Cost of illness in Sweden (million SEK in 2005 years prices)

<table>
<thead>
<tr>
<th>Illness</th>
<th>Year</th>
<th>Direct cost</th>
<th>Indirect costs</th>
<th>Total cost</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>2004</td>
<td>8 786 (35%)</td>
<td>16 033 (65%)</td>
<td>24 819</td>
<td>[146]</td>
</tr>
<tr>
<td>Stroke</td>
<td>1991</td>
<td>9 672 (76%)</td>
<td>2 999 (24%)</td>
<td>12 671</td>
<td>[147]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1994</td>
<td>2 767 (43%)</td>
<td>3 709 (57%)</td>
<td>6 475</td>
<td>[148]</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2002</td>
<td>920 (30%)</td>
<td>2 163 (70%)</td>
<td>3 083</td>
<td>*</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1994</td>
<td>417 (21%)</td>
<td>1 539 (79%)</td>
<td>1 956</td>
<td>[149]</td>
</tr>
<tr>
<td>Brain tumours</td>
<td>1996</td>
<td>379 (26%)</td>
<td>1 100 (74%)</td>
<td>1 479</td>
<td>[150]</td>
</tr>
</tbody>
</table>

* Paper I.

The value of indirect costs associated with breast cancer in the study was estimated based on human capital theory. The friction cost method has been suggested as an alternative method when estimating indirect costs. Compared to human capital theory, estimates using the friction cost method are substantially lower, amounting to approximately 12% of the indirect costs estimated with human capital theory. Although the friction cost method has been strongly criticised on the grounds that it is based on implausible assumptions not supported by neoclassical economic theory[47], it highlights the fact that the choice of method can have an important impact on the results. Using methods estimating the marginal value of production higher or lower than human capital theory would thus substantially alter the estimates of indirect costs due to breast cancer.

When estimating the direct costs of breast cancer, the unit cost (price) used for the different resources (e.g. screening or working year lost) can have a considerable impact on the result. An example of this is value of a working year lost, where we used a unit cost of 292 900 SEK. Instead using a unit cost of 250 000 SEK would result in a reduction of the estimated total cost of breast cancer by 217 million SEK.
An estimate of the intangible cost of breast cancer was also included in the study. Intangible costs represent the value associated with a reduction or an improvement in health, and one way of quantifying the reduction in health caused by disease is to estimate the number of QALYs lost due to that disease. The study estimated that a total of 10,956 QALYs were lost due to breast cancer in Sweden in 2002. Using a value per QALY of 600,000 SEK thus results in approximately 6.6 billion SEK of intangible costs. However, as previously mentioned, values ranging from 190,000 SEK and 3,200,000 SEK per QALY have been suggested[51]. Since the value of a QALY used in the estimate has such a substantial impact on the result, the estimate of intangible costs should be interpreted with caution.

The usefulness of cost of illness studies has long been a topic of debate[50, 151-153]. One of the arguments has been that since no comparison of alternative actions with respect to their costs and consequences is performed, cost of illness studies have no policy relevance. Another argument has been that cost-of-illness studies can lead to confusion in the priority setting. If a disease is found to be costly, should more or less resources be spent on the disease? Although it is true that cost of illness studies cannot be used as a basis for resource allocation decisions, they can still provide valuable information about how resources are spent and lost due to a disease. The magnitude of the different costs associated with a disease and where these costs arise can be an important aspect of understanding the impact of a disease on the health care system as well as on society. Moreover, successive cost of illness studies can be used to see how the cost structures change over time, due to changes such as the introduction of new medical technology, as well as to indicate where most benefits for the future can be found.

Investments in prevention and treatment that reduce breast cancer morbidity and mortality might cause a future shift in the cost structures, by reducing the indirect costs of breast cancer at the expense of increasing the direct medical costs. The present study could serve as a baseline for analysing this development.
8.2 COSTS AND QUALITY OF LIFE IN DIFFERENT STATES OF BREAST CANCER

Costs and health-related quality of life are important features of economic evaluations, and data for estimation of these parameters can be collected in different ways. Randomised clinical trials have become the standard for establishing the efficacy and safety of new therapies. Collecting health economic data prospectively alongside a randomised clinical trial is usually referred to as “piggyback”. The advantages of this approach include the possibility of a low marginal cost of data collection, high internal validity, as well as having patient-specific data on both costs and outcome for the economic evaluation. However, there are also drawbacks associated with collecting health economic data as part of a trial that has primarily been designed for clinical purposes. The comparison therapy might not be the most relevant for economic evaluation (e.g., placebo instead of the current standard of care). The trial might also be powered for a different primary outcome measure, resulting in an inadequate sample size and/or inadequate follow-up with respect to the health economic variables. Another drawback includes the risk of protocol-driven costs and outcomes (e.g., protocol-specified outpatient visits that would not occur in routine clinical practice) that bias the results. In addition, costs are specific to a certain health care system. Some countries might not be represented in international clinical trials, or only represented by few patients, making the health economic data gathered in the trial insufficient for an economic evaluation in that particular setting. The use of outcome measures that are more detailed than those used in routine clinical practice might also change clinical practice and thus bias the results. Another issue is the stringent inclusion and exclusion criteria that are normally used in clinical trials, which might bias results. These factors contribute to limit the external validity, i.e., the generalisability of the findings to other patients than those in the trial.

An alternative approach to overcome the drawbacks associated with “piggyback” data collection is to collect the data in a separate observational study. Naturalistic observational studies are designed to collect data from patients in normal clinical practice while, at the same time, interfering as little as possible with the normal clinical work. The trade-off when using a naturalistic observational study is a lower degree of internal validity in exchange for a higher degree of validity for the specific decision situation at hand.

Paper II found that the total cost was substantially higher for patients in their first year after primary breast cancer, patients in their first year after a recurrence, and patients with metastatic disease compared to patients in their second and following years after a primary breast cancer or recurrence. This seems reasonable since surgery, radiotherapy, and systemic therapy are concentrated within the first year following a primary breast cancer or recurrence, as well as the palliative treatment given to patients with metastatic disease. For patients aged below 65, indirect costs were found to constitute a majority of the total costs. This is consistent with the findings in Paper I. Indirect costs followed the same pattern as total inpatient and outpatient costs, with patients in their first year after primary breast cancer, patients in their first year after a recurrence, and patients with metastatic disease having higher indirect costs compared to patients in their second and following year after a primary breast cancer or recurrence.
This is consistent with previous studies that have found the negative impact on labour supply due to breast cancer to be caused by treatment related symptoms[154].

The HRQoL was estimated using both the EQ-5D and a direct TTO question. For all disease states, the reported TTO values were higher than the corresponding EQ-5D index values. The finding that social tariffs generate lower values than direct TTO measurements of the actual health state is consistent with previous studies[145, 155]. The study also found that all different disease states reported both lower TTO values and EQ-5D index values compared to an age and sex matched Swedish population[145]. An analysis of the different dimensions of the EQ-5D questionnaire found that patients in all the disease states consistently reported the highest percentage of moderate and severe problems for the dimensions pain/discomfort and anxiety/depression. This seems to indicate that it is pain/discomfort and anxiety/depression that are the main factors behind the reduction in HRQoL among breast cancer patients.

Patients in their first year after primary breast cancer reported the largest absolute difference between EQ-5D index value and TTO value. A total of 71% of the patients in this state reported moderate to severe problems with pain and discomfort. Even so, a majority of the patients in their first year after primary breast cancer reported a TTO value of 1, implying that their current health state was equivalent to full health, free from disease and pain. One reason for this inconsistency might be that patients in their first year after breast cancer only consider themselves to be temporarily ill, hence making them unwilling to sacrifice time for an increase in quality of life, since they believe that this increase will occur anyway. Patients with metastatic disease consistently reported the lowest HRQoL, independently of the method used. Compared to the other states, patients with metastatic breast cancer reported a higher degree of problems with pain/discomfort as well as mobility. This seems reasonable since certain metastases can be very painful, sometimes to the point of impeding the patient’s ability to walk. Moreover, the toxicity associated with many of the systematic therapies frequently administered to patients with metastatic disease would further tend to increase the problem of pain/discomfort.

A limitation of Paper II and Paper III is that all the patients were recruited from the same outpatient clinic. This meant that our patient sample was restricted to patients living and receiving care in a specific geographic area of Sweden. This might contribute to decrease the generalisability of the results to the rest of Sweden. However, oncology services are concentrated to a few clinics and the population served by this clinic (Radiumhemmet at Karolinska University Hospital) comprise the larger part of the 1.9 million inhabitants in Stockholm County. Another limitation of Paper II and Paper III was our selection method. For logistic reasons, we chose to include consecutive patients coming for treatment at Radiumhemmet at Karolinska University Hospital. It is possible that this causes a selection towards non-metastatic patients with more sever disease symptoms, since these patients are more likely to come for treatment at the outpatient clinic. This selection method also excludes breast cancer patients admitted to hospital, which might cause a selection bias toward metastatic breast cancer patients with less severe disease symptoms than the average metastatic breast cancer patient.
8.3 COST-EFFECTIVENESS IN THE METASTATIC SETTING

When a new breast cancer drug is being developed, the initial clinical trials are usually performed on metastatic breast cancer patients. In clinical trials, trastuzumab was found to be associated with a statistically significant increase in the time to progression as well as overall survival, leading to the approval by the FDA in 1998 for the treatment of HER2 positive metastatic breast cancer. However, due to the high costs of trastuzumab treatment, the cost-effectiveness of the drug was not obvious. An initial cost-effectiveness analysis found that despite the high costs of trastuzumab, it could be considered a cost-effective treatment for metastatic breast cancer patients[112]. However, two subsequent cost-effectiveness analyses found the incremental cost-effectiveness ratio of trastuzumab treatment for metastatic breast cancer patients to be higher than what is normally considered cost-effective[113, 114]. In Paper IV, a cost-effectiveness analysis of trastuzumab and chemotherapy compared to chemotherapy alone for patients with metastatic breast cancer was performed based on the latest clinical trial data and Swedish data on costs and quality of life presented in Papers II and III.

Table 9. Comparison of key model variables

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 testing included in analysis</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Model type</td>
<td>Markov</td>
<td>No model</td>
<td>Markov</td>
<td>Markov</td>
</tr>
<tr>
<td>Difference in time to progression between trastuzumab and chemotherapy compared to chemotherapy alone, months</td>
<td>5.4a</td>
<td>1.7 – 4.9b</td>
<td>3.9c</td>
<td>5.6d</td>
</tr>
<tr>
<td>Difference in overall survival between trastuzumab and chemotherapy compared to chemotherapy alone, months</td>
<td>9.8a</td>
<td>8.4 – 3.7b</td>
<td>Not stated</td>
<td>14.6d</td>
</tr>
<tr>
<td>Is cross-over taken into consideration</td>
<td>Yes</td>
<td>No</td>
<td>To some extent</td>
<td>Yes</td>
</tr>
<tr>
<td>Utility in progressive disease</td>
<td>0.33</td>
<td>-</td>
<td>0.49</td>
<td>0.685</td>
</tr>
<tr>
<td>Cost in progressive metastatic disease (in year 2005 SEK)</td>
<td>2 360</td>
<td>-</td>
<td>12 380</td>
<td>9 960</td>
</tr>
<tr>
<td>Cost per QALY gained (in year 2005 SEK)</td>
<td>540 000</td>
<td>-</td>
<td>1 151 000</td>
<td>561 000</td>
</tr>
</tbody>
</table>

a Difference in mean time to progression (TTP) and mean overall survival (OS) estimated by Hornberger et al.
b Difference in median TTP and median OS used in the analysis by Norum et al.
c Not explicitly stated. Based on the difference in median TTP between trastuzumab and paclitaxel compared to paclitaxel alone from the study by Slamon et al.
d Difference in median TTP and median OS reported in the study by Marty et al.
The analysis in Paper IV indicated that HER2 testing followed by trastuzumab and chemotherapy for patients with HER2 positive metastatic breast cancer was a cost-effective treatment option compared to chemotherapy alone. Table 9 compares key differences between the previously published studies and the study in Paper IV.

Both Paper IV and the study by Elkin et al included HER2 testing in the cost-effectiveness analysis, whereas the study by Hornberger et al and Norum et al did not. As can be seen in Table 9, the difference in time to progression and overall survival between trastuzumab and chemotherapy compared to chemotherapy alone used in the analyses varies between the different studies. There are two main reasons for this discrepancy. One is that Paper IV is based on the clinical study by Marty et al[37], which compares trastuzumab and docetaxel with docetaxel alone, while the studies by Hornberger et al and Elkin et al are based on the study by Slamon et al[36], which compares trastuzumab and paclitaxel with paclitaxel alone. The study by Norum et al was based on several different clinical trials, although the study by Marty et al was not included. The other reason is how crossover between the different treatment arms is handled in the different analyses. In the study by Slamon et al[36], 66% of the patients in the chemotherapy alone arm crossed over and received trastuzumab after disease progression. Since it is chemotherapy alone, and not chemotherapy alone with possible crossover to trastuzumab that is the relevant comparator, using the overall survival for patients that have crossed over would tend to underestimate the real difference in overall survival between trastuzumab and chemotherapy compared to chemotherapy alone. This underestimation of survival differences between the two treatment arms would then tend to lead to an overestimation of the cost per QALY gained. Hornberger et al[112] had access to trial data and could therefore adjust for the crossover in their study. Elkin et al[113] acknowledged the problem of crossover in the trial, and to some extent adjusted for this in their analysis. The study by Norum et al[114] did not adjust for crossover in the trial. Since the survival difference between the two treatments arms has an important influence on the cost per QALY gained, the difference in how crossover was handled could explain some of the inconsistency in the results between the different cost-effectiveness analyses.

There was also a large difference in the utilities used for the health state progressive metastatic disease in the different studies. This difference is most likely due to the methodology used to collect utility data. The utility estimates used by Hornberger et al and Elkin et al were elicited from nurses, whereas the utility estimates used in Paper IV were based on the EQ-5D response from Swedish breast cancer patients. Sensitivity analysis in Paper IV found that utility estimates used for progressive metastatic disease had an important influence on the estimated cost per QALY gained, with the utility estimate being inversely correlated to the cost per QALY gained. This could further help explain the differences in results between the different studies.
Looking at the cost for patients with metastatic disease, we again observed large variations between the different studies. A low cost for progressive disease is associated with a smaller difference in total costs when comparing trastuzumab and chemotherapy with chemotherapy alone, which contributes to reducing the cost per QALY gained. The study by Hornberger et al had the lowest cost for patients with progressive metastatic disease by far, about 20% of the cost applied by Elkin et al. This low cost for patients with progressive metastatic disease, together with the fact that they adjusted for the crossover between treatment arms, is likely to be the main reason for the favourable cost-effectiveness ratio found by Hornberger et al, despite their rather low utility for patients with progressive metastatic disease. In contrast, Elkin et al adjusted for crossover between treatment arms to some extent, used utility estimates that were substantially lower than the estimates used in Paper IV, and had the highest cost for patients with progressive metastatic disease of the different studies. These are likely to be the main factors contributing to Elkin et al estimating a cost per QALY gained that is substantially higher compared to Paper IV and the study by Hornberger et al.
8.4 COST-EFFECTIVENESS IN THE ADJUVANT SETTING

After the positive clinical results of trastuzumab on metastatic breast cancer, clinical trials of adjuvant trastuzumab treatment were initiated. These clinical trials included more than 13,000 randomized patients and compared adding trastuzumab for one year to adjuvant chemotherapy compared with chemotherapy alone. Results from the clinical trials have shown that adding adjuvant trastuzumab to adjuvant chemotherapy results in a statistically significant reduction of breast cancer relapse and improved overall survival. Based on these results, Trastuzumab was approved by the FDA in 2006 for adjuvant treatment of patients with HER2 positive early breast cancer.

Previously published cost-effectiveness analyses have all found adjuvant trastuzumab in addition to adjuvant chemotherapy to be a cost-effective treatment option compared to chemotherapy alone. The analysis in Paper V evaluated the cost-effectiveness of HER2 testing and one year of adjuvant trastuzumab after adjuvant chemotherapy for HER2 positive patients compared to chemotherapy alone, and found that adjuvant trastuzumab was a cost-effective treatment option. This is consistent with previously published studies. However, there are major differences in the details of the different studies, despite the consistency of results. These are highlighted in table 10.

Paper IV included HER2 testing in the cost-effectiveness analysis, whereas the other studies did not. Two factors that substantially influenced the cost-effectiveness of adjuvant trastuzumab were the relative risk reduction caused by adjuvant trastuzumab and the duration of trastuzumab’s benefit. Liberato et al[118] and Kurian et al[117] both based their relative risk reduction on the combined analysis of the NSABP B-31 and NCCTG N9831 trials[32]. However, their assumption about the duration of treatment benefit differs. Liberato et al assumed that the benefit of trastuzumab would persist only for 5 years, whereas Kurian et al assumed a one-third decrease in the relative risk reduction in years 2-4, and an additional one-third decline in years 5-10, with values held constant after year 10. In Paper V, the relative risk reduction caused by adjuvant trastuzumab was based on the HERA trial[34]. The relative risk reduction reported in the HERA trial was lower compared to the combined analysis reported by Romond et al[32]. This could be due to the fact that trastuzumab was given after chemotherapy, as opposed to in combination. Another reason could be the possibility of control patients in the HERA trial having the option to switch to trastuzumab treatment once it emerged that there was a significant disease-free survival in favour of 1 year’s treatment with trastuzumab compared to observation based on a median follow-up of 1 year. In Paper V, the duration of the trastuzumab’s benefit was assumed to be persistent, primarily based on findings of persistent effects of adjuvant tamoxifen[25]. However, the influence of reducing the duration of trastuzumab benefit was explored in a sensitivity analysis.

Assumptions about the annual risk of relapse were markedly different between the studies. Liberato et al assumed an annual risk of relapse for years 2 – 5 that was more than twice as high as compared to the risk used in the analysis in Paper V. Kurian et al also assumed an annual risk of relapse for years 2 – 5 that was substantially higher compared to Paper V.
### Table 10. Comparison of key model variables

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 testing included in analysis</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Relative risk of recurrence associated with trastuzumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.48</td>
<td>0.48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.64</td>
</tr>
<tr>
<td>Year 2-5</td>
<td>0.48</td>
<td>0.66&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.64</td>
</tr>
<tr>
<td>Year 6-10</td>
<td>1</td>
<td>0.75&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.64</td>
</tr>
<tr>
<td>Year &gt;10</td>
<td>1</td>
<td>0.75&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.64</td>
</tr>
<tr>
<td>Annual risk of relapse without trastuzumab, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.020</td>
<td>0.081&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.076&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 2-5</td>
<td>0.110</td>
<td>0.082&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.051&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year 6-10</td>
<td>0.034</td>
<td>0.047&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.043&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Year &gt;10</td>
<td>0.027</td>
<td>0.019&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.039&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Local recurrences considered separately from metastatic recurrences</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Patients receiving adjuvant trastuzumab receiving trastuzumab if metastatic disease %</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Duration of trastuzumab at the time of metastatic recurrence, months</td>
<td>9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Median survival with metastatic disease, months</td>
<td>25</td>
<td>25</td>
<td>18&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Utility in metastatic disease</td>
<td>0.580</td>
<td>0.550&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.685</td>
</tr>
<tr>
<td>Patient body weight, kg</td>
<td>60</td>
<td>Not reported</td>
<td>67</td>
</tr>
<tr>
<td>Indirect costs included</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Timeframe, years</td>
<td>15</td>
<td>Not reported</td>
<td>Life-time</td>
</tr>
<tr>
<td>Cost per QALY gained (in year 2005 SEK)</td>
<td>138 000</td>
<td>299 000</td>
<td>385 000</td>
</tr>
</tbody>
</table>

<sup>a</sup> Not explicitly stated. Based on the study by Romond et al.
<sup>b</sup> Not explicitly stated. Calculated based on the stated increase in relative risk reduction.
<sup>c</sup> Adapted from the study. Based on the average value for the relevant years.
<sup>d</sup> Average values for a HER2 positive woman aged 55.
<sup>e</sup> Only for HER2 positive patients that have not received adjuvant trastuzumab. Assumed 9 months since the median number of doses was 36 (one per week) in the Shumon study.
<sup>f</sup> For a 55 year old woman.
<sup>g</sup> All types of breast cancer recurrence.
The different models also took different approaches on how patients with metastatic disease were handled. Liberato et al assumed that only women who initially did not receive adjuvant trastuzumab would get trastuzumab in the metastatic setting. In contrast, Kurian et al assumed that both patients that had received adjuvant trastuzumab as well as patients that did not receive adjuvant trastuzumab would get trastuzumab in the metastatic setting. In the base case of Paper V, it was assumed that HER2 positive patients with metastatic disease had the same outpatient drug cost as patients that were HER2 negative. Sensitivity analysis showed that neither assuming trastuzumab treatment for all HER2 positive patients in the metastatic setting, nor that only trastuzumab naïve HER positive patients were give trastuzumab in the metastatic setting, would cause the cost per QALY gained to exceed what is normally considered cost-effective.

 Neither the Liberato et al nor Kurian et al included indirect costs in their analysis, even though Kurian et al stated that they performed their analysis from a societal perspective. Paper V included estimates for indirect costs in the model, based on the findings of Paper II. Sensitivity analysis showed that not including indirect costs would result in a slight increase in the cost per QALY gained. The time frame of the different studies did also differ, with Liberato et al using a fifteen-year time frame compared to a lifetime time frame in Paper V. The time frame used in the article by Kurian et al was not explicitly stated, but it appears that they used a life-time perspective.

The reason why the results of the different studies are consistent despite the major difference in the details of the models is that the different assumptions influence the cost per QALY gained in opposite directions. The larger relative risk reduction associated with adjuvant trastuzumab utilised by Liberato et al, the higher risk of relapse, and the lower utility for patients with metastatic disease would tend to decrease the cost per QALY gained compared to Paper V, while the lack of indirect costs, the shorter duration of trastuzumab benefit, and the shorter time frame of the analysis would tend to increase the cost per QALY gained compared to Paper V. The higher risk of relapse used by Kurian et al, the inclusion of trastuzumab treatment for all patients with metastatic disease, the lower utility for patients with metastatic disease, and the initially larger relative risk reduction associated with an adjuvant trastuzumab would tend to decrease the cost per QALY gained compared to Paper V, while the progressive reduction in the relative risk reduction associated with adjuvant trastuzumab, and the lack of indirect costs, would tend to increase the cost per QALY gained compared to Paper V.

In addition to the conclusions about the cost-effectiveness ratio of adjuvant trastuzumab derived from the analyses in Paper V and the studies by Liberato et al and Kurian et al, an important aspect is the insights these studies provide about which factors that have a major impact on the results. Uncertainty concerning the relative risk reduction of breast cancer relapse and the duration of trastuzumab benefit can have a substantial influence on the cost per QALY gained for adjuvant trastuzumab. Therefore, it is important that successive economic evaluations of adjuvant trastuzumab are performed after further clinical follow-up and/or new health economic data become available.
8.5 MODELLING IN ECONOMIC EVALUATIONS

The goal of economic evaluations is to assist in decisions about allocation of resources to improve health, within or outside the health care system. As new therapies are developed and introduced on the market, clinical trials that gather data on efficacy and safety are performed. In this initial phase, there is often a lack of long-term follow-up, but it might not be possible or efficient to postpone a decision about pricing, reimbursement and use until more evidence has been gathered. In the initial phase, the decision will therefore have to be made using the best available information. It is essential to use all available relevant evidence when performing economic evaluations. However, since all relevant information will rarely come from one source, it is usually necessary to use information from a wide range of disparate sources. By using a model that can combine available data from clinical trials with epidemiological data and health economic data from other sources, it is possible to obtain a first estimate of the cost-effectiveness of the new therapy, as well as the uncertainty around the estimate. As time progresses, more information about the long-term effects of the new therapy is generated. As this new information is generated, it can be incorporated into the model in order to give more precise estimates of the cost-effectiveness. However, as time progresses, other new treatment options might also be introduced, which can have a substantial influence on the economic evaluation. Economic evaluations can therefore be described as an iterative process that is trying to hit a constantly moving target. An advantage of a model is that it can use several different types of data to produce a best estimate of cost-effectiveness at any given point in time of the life cycle of a therapy.

For a model to be useful in assisting decisions about allocation of resources to improve health, all relevant costs and outcomes have to be included in the model. The evaluations also have to take into consideration all relevant comparators for the given treatment, as well as adopting a time-horizon that is sufficiently long to take all relevant costs and outcomes for the different treatment options under evaluation into consideration. Furthermore, it is important that the model accurately represents available data. This can be verified by checking that the model outputs in terms of number of events, total costs etc are consistent with data from observational studies.

The ability to accurately predict future costs and outcomes is an important property of a good model. However, the model’s predictive validity must be assessed based on the benefits in terms of improving the model for decision making, against the possible consequences of a delayed flow of information if a less effective and more costly treatment is used while data are collected to assess validity[156]. Since the main goal of a model is not necessarily to accurately predict the future, but rather to assist in decision making, it might be inappropriate to demand predictive validity in certain circumstances. A complementary aspect in model verification is to verify if the model leads to similar conclusions as independently developed models with the same scenario, and if they do not, that the differences can be explained in a logical way.
8.6 TARGETED THERAPIES AND PERSONALISED MEDICINE

Trastuzumab is usually referred to as a targeted therapy, and it is one of several examples of the current integration of molecular oncology and molecular diagnostics. Many believe that this integration of molecular oncology and molecular diagnostics will continue to influence oncology drug discovery and development, and that the number of targeted therapies will continue to increase in the future[157]. There is no single definition of what constitutes a targeted therapy. The FDA has defined targeted therapy as a drug with an approved label with a specific reference to a simultaneously or previously approved diagnostic test that must be performed before the patient can be considered eligible to receive the drug. Trastuzumab falls into this definition. Using a broader definition, targeted therapies can be defined as drugs with a focused mechanism that specifically acts on a well-defined target or biologic pathway that, when inactivated, causes regression or destruction of the malignant process[157]. This broader definition would include both hormonal-based therapies and monoclonal antibodies for breast cancer treatment. Traditionally, physicians have based their diagnosis on observable manifestations of a disease, and then proceeded to treat the disease according to the symptoms. Advances in molecular biology have made it possible to not only analyse the observable symptoms of a disease, but also analysing detailed information about a patient’s genotype, level of gene expression, proteins, and metabolites. It is this use of a patient’s molecular information in addition to normal analysis of observable symptoms to guide treatment choice, dosing, type of administration, length of treatment, and monitoring of treatment effect and adverse side-effects that is usually referred to as personalised medicine.

In some areas of breast cancer treatment, targeted therapies and personalised medicine have been in use for some time. Tamoxifen, first approved by the FDA in 1977, is effective for hormone receptor-positive breast cancer. The use of hormone receptor status for assigning patients to tamoxifen treatment was an early example of how the use of a patient’s molecular information could be successfully applied to guide a targeted therapy. The use of immunohistochemical (IHC) tests and/or fluorescence in situ hybridization (FISH) tests to guide trastuzumab treatment is another example of a patient’s molecular information being successfully applied to guide a targeted therapy.

Diagnostic tests that are used to gather information that can influence the treatment choice should be considered as part of the therapy in economic evaluations, since both costs and outcomes can be influenced by the test result. This means that the cost, sensitivity and specificity of the diagnostic tests should be included in the economic analysis. Not including the diagnostic test characteristic, and instead assuming that physicians have perfect information about which patients will benefit from treatment at no additional cost, would tend to underestimate the cost per QALY gained for a given treatment requiring a diagnostic test to identify eligible patients. This underestimation will be greater if the diagnostic test is expensive and has poor sensitivity and specificity. Assuming that the clinical importance, costs, and quantity of diagnostics tests will increase over time, diagnostic tests will come to play a more significant role in the health care system. A systematic evaluation of the effectiveness and cost-effectiveness of integrated diagnostic tests and therapies could therefore become increasingly important when deciding on resource allocation to maximise health.
8.7 POLICY IMPLICATIONS

Assuming that the willingness to pay for a QALY is 655 000 SEK in a Swedish setting, HER2 testing and trastuzumab treatment were found to be a cost-effective treatment for both patients with metastatic breast cancer and patients with early breast cancer. If the willingness to pay per unit of effect is used as the decision rule, then FISH testing with trastuzumab and chemotherapy for FISH positive patients and chemotherapy alone for the remaining patients should be adopted as the testing and treatment strategy of choice for patients with metastatic breast cancer. In the adjuvant setting, FISH testing with one-year adjuvant trastuzumab after adjuvant chemotherapy for FISH positive patients and no additional adjuvant therapy after adjuvant chemotherapy for the remaining patients should be implemented as the testing and treatment strategy of choice for patients with early breast cancer.

An alternative approach to decide which treatment strategies should be chosen to maximise health is to use the budget as a decision rule. The first step would then be to decide the budget that we are willing to spend on breast cancer patients and, second, to order all treatments according to their ICER. The treatment with the lowest ICER would then be implemented first, with independent treatments being added or mutually exclusive treatments being replaced with more effective treatments until the budget is exhausted.

A possible outcome of using the budget as a decision rule could be that adjuvant trastuzumab is adopted as a viable treatment strategy, but that trastuzumab in the metastatic setting is not, due to the latter having a higher ICER. Using the budget as a decision rule also entails the possibility of different treatments for different patients within the same patient group, such as some patients with HER2 positive early breast cancer receiving adjuvant trastuzumab, while others do not. This case would most likely involve a bias towards treating younger patients with adjuvant trastuzumab in favour of older patients, due to the more favourable ICERs found for younger patients. Using the budget as a decision rule would therefore raise a number of important ethical issues concerning who should get priority for treatment.

Due to the ethical implications of using the budget as a decision rule, as well as the difficulties in deciding on a specific budget for breast cancer treatment and ordering all available treatment options according to their ICER, the willingness to pay for a unit of effect represents a more straightforward approach.
Using willingness to pay for a unit of effect as a decision rule, trastuzumab treatment should be given to all eligible patients within the entire Swedish health care system, both in the metastatic setting as well as in the adjuvant setting. However, this implementation would be likely to increase the budget needed for breast cancer treatment. There has been a steady increase in the sales of trastuzumab, with a three-fold increase in the last two years from 64 million SEK per year in 2004 to 193 million in 2006[158, 159]. A wide-spread adoption of adjuvant trastuzumab treatment is likely to further increase the sales of trastuzumab. This increase in breast cancer treatment costs could either be covered by transferring resources from another part of the health care budget to breast cancer treatment, or by increasing the total health care budget. Another possible solution could be a price decrease in trastuzumab. A price decrease in trastuzumab would lessen the budget impact of trastuzumab treatment, possibly leading to better patient access to the drug.

Another policy relevant aspect concerns the indirect costs associated with breast cancer. Since indirect costs were found to constitute a substantial part of total breast cancer costs, it is important to include indirect costs in economic evaluations, since not doing so could bias the results. One example of this could be a therapy with little influence on survival or health related quality of life, but that brings a substantial reduction of the indirect costs arising from morbidity due to breast cancer. If an economic evaluation of this new therapy is conducted from a health care perspective and thereby limited to direct medical costs only, the new therapy might be dominated since it will have a higher cost and a similar outcome to its comparator. However, if the economic evaluation is conducted from a societal perspective, the result could be very different, possibly finding the therapy to be cost-effective or even cost-saving. A problem with this type of intervention is that a majority of the costs will be incurred by the health care system, while a majority of the cost-savings will occur outside the health care system. Since those who bear the costs do not benefit from the potential cost savings, there might be a reluctance within the health care community to implement this type of intervention. This highlights the importance of finding a system that can transfer at least some of the cost-savings of breast cancer therapy to those bearing the cost. It also highlights the importance of performing economic evaluations of breast cancer therapies from a societal perspective, since not including indirect costs could lead to substantial policy decisions.
9 CONCLUSIONS

The main findings of this thesis are:

- Breast cancer constitutes an important economic burden to society, amounting to approximately 3 billion SEK per year in Sweden. Indirect costs accounted for about 70% of the total cost of breast cancer, with the indirect cost of mortality being the main cost driver of indirect costs. Hospitalisation was the main cost driver for direct costs.

- The first year after primary breast cancer, the first year after recurrence, and metastatic breast cancer are associated with a substantial cost of breast cancer. For patients less than 65 years of age, indirect costs constitute the main part of the total cost of breast cancer.

- Breast cancer is associated with a reduction in health related quality of life. This reduction seems to be caused by pain and discomfort as well as anxiety and depression. The reduction is most pronounced for patients with metastatic breast cancer.

- Treatment with trastuzumab and chemotherapy compared to chemotherapy alone for metastatic breast cancer patients is indicated to be cost-effective.

- Treatment with one year of adjuvant trastuzumab after adjuvant chemotherapy compared to adjuvant chemotherapy alone for early breast cancer patients is indicated to be cost-effective.

- When evaluating the cost-effectiveness of a targeted therapy such as trastuzumab, it is important to take into consideration the costs, sensitivity, and specificity of the diagnostic test used to assign patients to therapy.

- Since indirect costs constitute an important part of the total cost of breast cancer, it is important that economic evaluations and cost of illness studies are performed from a societal perspective.
10 ACKNOWLEDGEMENTS

I have received plenty of help and support during the writing of this thesis. I would therefore like to express my warmest thanks to the following people:

Bengt Jönsson, supervisor, who gave me the opportunity to come to Stockholm and become a PhD student at the tender age of 22. I think it is quite safe to say that me writing this thesis is all your fault! Thank you for sharing you immense knowledge in health economics, and thank you for all the support you have given me, both inside and outside the academic world.

Nils Wilking, supervisor, for sharing you outstanding medical knowledge and enthusiasm.

Clas Rehnberg, my main supervisor, for your valuable contributions to this thesis and for guiding me through the administrative jungle at KI.

Niklas Zethraeus, comrade in arms at the Stockholm School of Economics, for never being too busy to offer a helping hand, and for always being willing to share your vast knowledge in health economics.

Ulla Wilking, for fruitful discussions and valuable help during the data collection process.

Johan Almbrandt, for your valuable help in collecting epidemiological data, as well as your valiant efforts to increase my knowledge of different types of beer.

Friends and colleagues at European Health Economics for all the good times at and outside work

Manu, Stef, and Thierry, for being the most excellent of friends, always making sure I remember that the most important thing in life is to enjoy it!

Sophie Berwick, for all your help, support, kindness and love. I couldn’t have done this without you.

Finally, I would like to dedicate this thesis to my family:

My sister, my brother-in-law, my nephew, my mom and my dad, for never ceasing to encourage me when things are difficult, and for always sharing my happiness in times of joy. You are the best. I love you all!
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