BREAST CANCER SURVIVORS:
INFORMATION NEEDS, ATTITUDES TOWARDS ILLNESS AND QUALITY OF LIFE

Birgitta Wallberg
The books one has written in the past have two surprises in store:
One couldn't write them again, and wouldn't want to

Jean Rostand, scientist and philosopher
ABSTRACT

Breast cancer (BC) is the most common female cancer. Only in Sweden about 7300 women are affected each year and 1500 die from the disease. Following progress in early detection and therapy there has been a marked improvement in survival and an increase in the number of BC survivors. This scenario has directed focus on the communication between the woman and her doctor, to meet information needs and to optimize the decision process about treatments. Quality of life issues among BC survivors is a clinical problem of growing magnitude.

The aims of this thesis were: to explore information needs among breast cancer survivors and their preferences for participation in treatment decisions; to elucidate the meaning of illness; to investigate attitudes towards clinical trials, benefits versus risks and the balance between quality and length of life; to assess health related quality of life (HRQoL) with and without hormone replacement therapy (HRT).

Structured interviews were performed within 18 months after diagnosis in 201 BC patients. Using validated instruments and questionnaires individual profiles for information needs, preferred/actual role in treatment decision and meaning of illness were explored. Samples of women from the randomized prospective Stockholm trial on HRT after BC were interviewed about participation in clinical trials and about HRQoL.

Information needs are strong among breast cancer survivors with the highest priority for disease specific items of information – chance of cure, stage of disease and treatment options. When offered participation in a clinical trial with HRT the top priorities of information were about hard facts related to HRT – risk of recurrence, new research about HRT and evidence about advising women treated for breast cancer against HRT. Breast cancer survivors prefer a collaborative role with their physician in treatment decisions. As the perceived meaning of illness most women chose challenge with enemy and irreparable loss as second and third choices.

Women participating in a clinical trial with HRT were more prepared to accept uncertainties and risks, including the risk of a recurrence in breast cancer, if their quality of life or general health was improved. They also had a more altruistic attitude compared to those who declined participation. Women made rational decisions whether to participate or not – participants had a lower risk of recurrence in breast cancer than non-participants.

Breast cancer survivors on HRT experienced an improvement in Insomnia compared to the control group without treatment. Within the HRT-group there was an improvement over time for several quality of life variables: anxiety, depression, emotional, cognitive and social functions and for global quality of life. HRT added to tamoxifen significantly increased global quality of life compared to tamoxifen alone.

Breast cancer survivors represent a growing number of women with strong information needs. The communication between patients and health care providers should receive increased attention. There is a need for safe and effective strategies to improve HRQoL in breast cancer survivors.

Key words: Breast cancer, meaning of illness, information needs, clinical trials, HRT, HRQoL.

ISBN 978-91-7409-875-4
LIST OF PUBLICATIONS

I. Information needs and preferences for participation in treatment decisions among Swedish breast cancer patients
   Birgitta Wallberg, Helena Michelson, Marianne Nystedt, Christina Bolund, Lesley F. Degner and Nils Wilking.

II. The meaning of breast cancer
    Birgitta Wallberg, Helena Michelson, Marianne Nystedt, Christina Bolund, Lesley Degner and Nils Wilking

III. Hormone replacement therapy after breast cancer: attitudes of women eligible in a randomized trial
    Birgitta Wallberg, Eva von Schoultz, Christina Bolund, Jonas Bergh and Nils Wilking
    Climacteric 2009; 12:478–489

IV. Health-related quality of life during hormone therapy after breast cancer: a randomized trial
    Mia Fahlén, Birgitta Wallberg, Eva von Schoultz, Kjell Carlström, Gunvor Svensson, Nils Wilking and Yvonne Brandberg.
    Climacteric 2010; Early online, 1–8
TABLE OF CONTENTS

1 INTRODUCTION ..................................................................................................................62
  1.1 Breast cancer survivors ...............................................................................................1
  1.2 Epidemiology of breast cancer ..................................................................................1
    1.2.1 Breast cancer incidence ....................................................................................1
    1.2.2 Breast cancer mortality ....................................................................................3
  1.3 Risk factors and hormones .......................................................................................5
  1.4 Diagnosis of breast cancer .......................................................................................7
  1.5 Treatments of early breast cancer ............................................................................7
    1.5.1 Surgery ............................................................................................................7
    1.5.2 Radiotherapy ..................................................................................................8
    1.5.3 Medical therapy ...............................................................................................8
    1.5.4 Prognostic factors ...........................................................................................10
    1.5.5 Predictive factors ...........................................................................................11
    1.5.6 The prize of progress ....................................................................................12
  1.6 Information needs and patient participation in treatment decisions .................12
  1.7 Patients participation in treatment decisions .......................................................16
  1.8 The meaning of breast cancer .................................................................................18
  1.9 HRT and breast cancer ............................................................................................20
  1.10 Patients in research and clinical trials .................................................................21
    1.11 Health-related quality of life (HRQoL) ...............................................................25
2 AIMS .................................................................................................................................27
3 PATIENTS, MATERIALS & METHODS ........................................................................28
  3.1 Patients ....................................................................................................................28
  3.2 Interventions ..........................................................................................................28
  3.3 Statistical analyses .................................................................................................30
4 RESULTS ..........................................................................................................................31
  4.1 Paper I ....................................................................................................................31
  4.2 Paper II ....................................................................................................................34
  4.3 Paper III ...................................................................................................................37
    4.3.1 Information needs ............................................................................................37
    4.3.2 Patient participation in research and clinical trials ........................................39
    4.3.3 Patient roles ....................................................................................................41
  4.4 Paper IV ..................................................................................................................42
5 DISCUSSION ....................................................................................................................46
  5.1 Information needs ....................................................................................................46
  5.2 Patient participation in treatment decisions ..........................................................47
  5.3 The meaning of breast cancer ...............................................................................49
  5.4 Participants and non-participants in the Stockholm study .....................................51
  5.5 Attitudes to participation in clinical trials ...............................................................51
  5.6 Health related quality of life in the Stockholm study .............................................52
6 GENERAL CONCLUSIONS ..............................................................................................55
7 CRITICAL ASSESSMENTS AND FUTURE PROSPECTS ........................................57
8 Acknowledgements .......................................................................................................59
9 References .......................................................................................................................62
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>HT</td>
<td>Hormone therapy</td>
</tr>
<tr>
<td>GNRH agonist</td>
<td>Gonadotropin-releasing hormone</td>
</tr>
<tr>
<td>ER</td>
<td>Oestrogen receptor</td>
</tr>
<tr>
<td>PR</td>
<td>Progesterone receptor</td>
</tr>
<tr>
<td>HER2</td>
<td>Human epidermal growth factor receptor 2</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire-C30</td>
</tr>
<tr>
<td>EORTC QLQ-BR23</td>
<td>European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer specific module - BR23</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 BREAST CANCER SURVIVORS

Breast cancer survivors is an increasing group of women. Approximately 80 000 alive Swedish women can (Lidgren, 2007) tell us about the day when everything was changed – the day when they were diagnosed with breast cancer. Many more are the relatives and friends of breast cancer survivors and all are affected by the disease in different ways. Breast cancer patient organisations are active, the exposure in mass media is intense, activity on the internet is massive.

In each meeting between the breast cancer patient and medical profession communication is established, almost always with exchange of information. This is a dynamic process affected by whom the patient is, where in the process she is and also by who the doctors and nurses are. It is a great challenge to take part in the information process and an important task to invest time and competence to meet the needs of the breast cancer patients. Breast cancer survivors can teach us a lot.

1.2 EPIDEMIOLOGY OF BREAST CANCER

1.2.1 Breast cancer incidence

Breast cancer is the most common cancer among women world wide and constitutes about 30% of all female cancers in Sweden (The National Board of Health and Welfare, 2009) (Fig 1).

Out of more than 51 000 cancer cases in Sweden in 2008 just around 7 300 were women diagnosed with breast cancer. The majority (54 %) of these women were under 65 years of age at the time of diagnosis, before retirement age, which contributes to a large health as well as economic burden of the disease. It should also be noted that 18 % of women were under 50 years of age (Fig 2) (The National Board of Health and Welfare, 2009).
Worldwide more than 1.2 million women develop breast cancer every year. Incidence rates are significantly higher in developed countries than in developing countries but are rapidly increasing in many newly industrialised countries due to rapidly changing lifestyles reflecting patterns in high incidence developed countries. An increased life expectancy in a country also contributes to an increased incidence of breast cancer (Wilkling and Kasteng, 2009).

Sweden is, as described, a country with a high incidence of breast cancer. The incidence varies considerably in different parts of the world and is highest in Western industrialised countries like the US, Canada, Australia, Western Europe and the Nordic countries (IARC scientific publications, 1992; Kelsey and Horn-Ross, 1993). The incidence has been increasing, in Sweden with about 1.2 % per year during the last 20 years but the increase in the recent 10-year period is weaker with an annual change of 0.8 % and for some age groups the increase has stopped (The National Board of Health and Welfare, 2009). Thus, the increase in incidence has changed and in some countries also resulted in a decreased incidence which will later be discussed. Increase is however still real most countries and not only based on the fact that people live longer or on more efficient diagnostics. The reason for the increase is not clear but a great deal points towards environmental exposures and lifestyle factors as probably also important.

Figure 2. Age-specific breast cancer incidence

Figure 3. Breast cancer incidence and mortality in the Nordic countries, cases per 100 000 women, age-adjusted
When groups of populations emigrate from low risk to high risk countries women in the next second and third generations develop the same risk pattern for breast cancer as women in their new home land. Extensive research has not been able to identify determining factors and subsequently neither found ways to prevent the disease.

1.2.2 Breast cancer mortality

Breast cancer mortality in Sweden has, contrary to incidence, been stable for many years and is now even decreasing (Fig 4). If demographic changes are taken into consideration, breast cancer mortality has decreased in average by 1 percent per year during the last 20 years. About 1 500 women have died from breast cancer in our country every year during the last decades at the same time as the incidence is increasing (The National Board of Health and Welfare, 2005a, b). Thus, more breast cancer patients are cured from the disease, the number of breast cancer survivors is increasing, prognosis is improving and has gradually improved since the 1960’s. In Sweden the five year relative survival rate has increased from 65 % (women diagnosed 1964-66) to 84 % (women diagnosed 1994-96) (Talback et al., 2003). For women diagnosed with breast cancer in the beginning of the 2000s the 5-year survival rate is expected to be 87% (Talback et al., 2004). The latest published data from the Stockholm County Council reports the 5-year relative survival rate to 90 % for women diagnosed between 2000 and 2004 (Fig 5 next page).

However, a 5-year perspective is not sufficient to estimate the rate of breast cancer patients that are actually cured, since some patients may experience relapses after having been relapse free for many years after diagnosis and first treatment. It is therefore relevant to look at 10-year or even 15-year survival rates in order to determine...
the actual outcomes in breast cancer. In Sweden the 10-year survival has increased from just over 50% at the beginning of the 1960s to up to 80% today (The National Board of Health and Welfare, 2007; Wilking and Kasteng, 2009) – just as in other countries with the best outcome in the treatment of breast cancer (Talback et al., 2004).

The results of breast cancer treatment in Sweden measured as survival of the disease belongs to the best in Europe (Sant et al., 2009). This means, as mentioned before, that an increasing number of women, today estimated to 80,000, live with a breast cancer diagnosis, including both cured and not cured patients (Lidgren, 2007). This increase in the prevalence of breast cancer depends on several reasons: the increase in the number of patients diagnosed with breast cancer and the number of patients cured, an increase of the population and an increase of older women in the population (The National Board of Health and Welfare, 2007). The prevalence of breast cancer is expected to continue to increase.

There are several factors that seem to explain this improvement. The two most important are earlier detection, due to mammography screening programmes, increased awareness among women, and more efficient adjuvant treatments with chemotherapy, radiation and endocrine treatment after radical surgery (Berry et al., 2005). In the study by Berry a technique with seven statistical models was used to assess the relative and absolute contributions of screening mammography and adjuvant treatment to the reduction in breast cancer mortality in the US from 1975 to 2000. The reduction attributed to screening was varied from 28 to 65 percent (median 46%) with adjuvant treatment contributing the rest.

In Sweden mammography screening programmes were introduced on a national basis in 1986, which is very early compared to most other nations. In different regions of Sweden programmes have been implemented successively between 1974 and 1997. Screening mammography significantly reduces breast cancer mortality by detecting small tumours even before they give clinical symptoms (Nystrom et al., 2002; Smith et al., 2004; Tabar et al., 2004).

According to the guidelines from the Swedish national board of health and welfare (Socialstyrelsen) the screening program is recommended to start at the age of 40 and end at 74.
1.3 RISK FACTORS AND HORMONES

“Why me?” is a very common question from women newly diagnosed with breast cancer. We can never give a straight answer. We do not know in the individual case but we know several risk factors that have been identified in epidemiological studies (Veronesi et al., 2005). The most important risk factor is age and thus an increase of the average length of life for women in a country contributes to an increased breast cancer incidence.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative Risk (RR)</th>
<th>High-risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt; 10</td>
<td>Elderly individuals</td>
</tr>
<tr>
<td>Age at menarche</td>
<td>3</td>
<td>&lt; 11 years old</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>2</td>
<td>&gt; 54 years old</td>
</tr>
<tr>
<td>Age at first full pregnancy</td>
<td>3</td>
<td>First child after the age of 40</td>
</tr>
<tr>
<td>Breastfeeding and parity</td>
<td>4.3 % RR reduction for every year of breastfeeding in addition to a 7 % RR reduction for every birth</td>
<td>Women who do not breastfeed</td>
</tr>
<tr>
<td>Use of exogenous hormones:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>1.2</td>
<td>Current users</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>1.66</td>
<td>Current users</td>
</tr>
<tr>
<td>Family history</td>
<td>≥ 2</td>
<td>Breast cancer in first-degree relative</td>
</tr>
<tr>
<td>Cancer in the other breast</td>
<td>&gt; 4</td>
<td>Previous breast cancer</td>
</tr>
<tr>
<td>Previous benign breast disease</td>
<td>4 – 5</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Geographical location</td>
<td>5</td>
<td>Developed countries</td>
</tr>
<tr>
<td>Body-mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>0.7</td>
<td>High body-mass index</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>2</td>
<td>High body-mass index</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1.07</td>
<td>7 % increase with every daily drink</td>
</tr>
<tr>
<td>Exposure to ionising radiation</td>
<td>3</td>
<td>Agnormal exposure to young girls &gt; 10 years old</td>
</tr>
</tbody>
</table>

**Hormone related factors – endogenous hormones**

There is strong evidence that endogenous sex hormone levels are of major importance in breast cancer aetiology. The breast cancer incidence shows a continuous increase by age, from 20 to 50 years. After the age of 50 when average women enter the postmenopausal state due to a loss of ovarian hormone production there is a slowing of the rate of increase in the incidence rate (Spicer and Pike, 1993)

Women who have undergone oophorectomy at the age of 30 have a much lower risk of breast cancer.
Early menarche, late menopause and nulli-parity which all include prolonged influence of estrogen have all been associated with increased breast cancer risk (Kelsey et al., 1993; Veronesi et al., 2005). Young age at first childbirth, several pregnancies, long term breastfeeding, all reduce the risk of breast cancer (Kelsey et al., 1993; Veronesi et al., 2005). Early menopause or oophorectomy are strongly protective and increases survival in breast cancer patients aged under 50 (EBCTCG, 1996; Spicer and Pike, 1993).

All these factors points at a connection with female sex hormones, but the connection is complex and yet far from being fully elucidated (Kelsey, 1993; Lambe, 1995; Pike et al., 1993).

The patho-physiological mechanisms underlying the development of breast cancer in general and estrogen/progestin associated carcinogenesis in particular, are incompletely understood.

**Hormone related factors – exogenous hormones**

Beginning in the 1960’s millions of women worldwide are treated with different combinations of estrogen and progestin for hormonal contraception or for alleviation of menopausal symptoms. Use of oral contraceptives in young women generates a small increase in the risk of breast cancer (Hazard ratio 1.2) that will disappear 10 years after treatment is stopped (EBCTCG, 1996; Veronesi et al., 2005).

A 40 year follow-up report from Great Britain reported no increase in risk of breast cancer but a decrease of 12 % in total cancer incidence (Hannaford et al., 2007; von Schoultz, 2009).

Women using Hormone Replacement Therapy (HRT) after menopause have an increased risk of breast cancer which seems to be duration-dependant (Beral, 2003; Chlebowski et al., 2003; Collaborative Group on Hormonal Factors in Breast Cancer, 1997). The risk is higher with a combination therapy of estrogen and progestin than with only estrogen (Chlebowski et al., 2003). The risk was normalized 3-5 years after HRT was stopped (Conner et al., 2008). The issue of HRT will be further discussed (page 20).

**Hereditary breast cancer**

The majority of all breast cancers are sporadic, 8 out of 9 breast cancer patients do not have a family history of the disease (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). About 5-10 % are attributed to known hereditary factors and the two susceptibility genes BRCA1 and BRCA2 (Weber and Garber, 1996). With mutations in these genes the life time risk of breast cancer is highly increased, for BRCA1-carriers 59% risk to develop breast cancer at the age of 50 and 86% risk at the age of 80. In addition there is also a “familial” breast cancer i.e. a history of breast cancer in one or more first or second-degree relatives without any known genetic mutation according to current knowledge but with an increased risk of breast cancer.

6
1.4 DIAGNOSIS OF BREAST CANCER

The recommended diagnostic approach in breast cancer is so called triple diagnostics including a clinical examination of the breasts and regional lymph nodes by a physician, radiological investigation (mammography, ultra sound) and a biopsy (sample of cells or tissue). Either a fine needle biopsy is taken for cytology or a core biopsy for histopathology to distinguish between invasive cancer and cancer in situ. Surgical biopsy is seldom necessary, but may be indicated in special cases. Biopsies from non-palpable lesions are taken with guidance by stereo-tactic mammography or ultra sound.

The value of Magnetic Resonance Imaging, MRI, of the breasts is not yet established. For women with a high hereditary risk to develop breast cancer surveillance with MRI of the breast has proved to be more sensitive than mammography but it is not yet known if it lowers mortality in this population (Leach et al., 2005; Warner and Causer, 2005; Warner et al., 2004). Thus, further research is needed to establish the value of MRI of the breast for women with hereditary risk of breast cancer as well as for women with average risk.

1.5 TREATMENTS OF EARLY BREAST CANCER

1.5.1 Surgery

Breast tumours in early stages are surgically removed. The surgical techniques include breast-conserving surgery (partial mastectomy, segmental resection, lumpectomy), mastectomy and axillary lymph node sampling and removal. In breast-conserving surgery, only a part of the affected breast is removed, how much depends on the size and location of the tumour. For most women with Stage I or II breast cancer, breast-conserving surgery in combination with radiotherapy is as effective as mastectomy (Fisher et al., 2002; Veronesi and Zurrida, 2009). Between 60 and 70 % of breast cancer patients have breast-conserving surgery (Hiotis et al., 2005). A mastectomy involves removing all of the breast tissue. Breast reconstruction after mastectomy can be performed at the time of tumour resection or later.

Information on the lymph node involvement (with or without tumour cells) is part of the staging process and the results will determine subsequent postoperative treatment recommendations. A sentinel lymph node biopsy is the identification and removal of the first lymph node(s) into which a tumour drains, which will most likely contain cancer cells if they have started to spread outside of the breast. Axillary lymph node dissection is performed when the sentinel node contains breast cancer cells and when there is a verified lymph node metastasis (by cytology/pathology) before surgery. Anywhere between 10 and 20 lymph nodes are removed in axillary dissection. If the sentinel node is free from cancer cells no axillary dissection is performed which decreases the risk of impaired lymph flow in the arm with a risk to develop a lymph oedema (Tsai et al., 2009).
1.5.2 Radiotherapy

Radiotherapy is treatment with high-energy rays or particles that destroy breast cancer cells remaining in the breast after breast-conserving surgery, on the chest wall after mastectomy or in the regional lymph node areas.

Breast-conserving surgery in patients with invasive breast cancer should be followed by radiotherapy in order to reduce loco-regional recurrences (Liljegren et al., 1999; Malmstrom et al., 2003; Veronesi et al., 2001). This means that the entire breast receives radiation with sometimes an extra boost of radiation given to the area in the breast where the cancer was removed. Radiotherapy has gained an increased importance, and a recent meta-analysis revealed that radiotherapy as a complement to surgery decreased the risk of loco-regional relapse by two-thirds compared to surgery alone and improved 15-year breast cancer survival of 5.4% after postoperative radiotherapy both after breast conserving surgery and mastectomy (Clarke et al., 2005).

Adjuvant radiotherapy is given daily during 3.5 to 6.5 weeks.

Technical innovations in radiotherapy after breast conserving surgery include the use of accelerated partial breast irradiation (APBI) which can be accomplished using interstitial, intra-cavitary, external-beam or intra-operative techniques. Clinical trials are underway comparing APBI to conventional techniques (Lee and Harris, 2009).

1.5.3 Medical therapy

Adjuvant medical treatment means systemic therapy given after surgery to patients with no evidence of residual cancer outside the breast or the lymph nodes with the purpose of destroying microscopic cancer cells that might remain in the body and cause recurrence of the disease. Adjuvant therapy after breast cancer consists of chemotherapy, endocrine therapy, and/or biological targeted therapies.

Chemotherapy inhibits cell growth by different mechanisms and thus reduces the rapid cell proliferation that is a characteristic of cancer cells. Endocrine therapies (tamoxifen, GNRH-agonists and aromatase inhibitors) block the effect of oestrogen or reduce hormone levels, and have effect in hormone sensitive breast cancer where tumour growth is stimulated by oestrogen (about two thirds of all cases). Biological targeted therapies selectively attack genetic expression that is typical for some types of cancer cells.

The recommendation of adjuvant treatment is guided by a risk-benefit assessment, weighting a patient’s risk of breast cancer recurrence against adverse effects of adjuvant treatment (Ravdin et al., 2001; Siminoff et al., 2006). Adjuvant treatment is covered in basically all treatment guidelines identified (Goldhirsch et al., 2009).

The first generation of adjuvant chemotherapy evolved during the 1970s. Adjuvant medical treatment in breast cancer has evolved over a 30-40 year period. Combination regimens, of two to three drug types, with different mechanisms of action are recommended as adjuvant chemotherapy in breast cancer. Better regimens have been developed over time and at present, chemotherapy regimens containing taxanes and...
anthracyclines have been demonstrated as the most effective (EBCTCG, 1998a, 2005; Ejlertsen et al., 2007; Henderson et al., 2003; Mamounas et al., 2005).

Endocrine therapy of breast cancer started with tamoxifen. Launched in 1975 and initially considered a costly treatment with limited effect, tamoxifen has been established as the most cost-effective cancer treatment to date and represents a major breakthrough in the treatment of breast cancer (Rutqvist et al., 1987).

Aromatase inhibitors (anastrozole, exemestane and letrozole), are now in part replacing tamoxifen for post-menopausal patients.

In pre-menopausal women ovarian ablation or suppression can be achieved by surgery, radiotherapy or medically by GNRH-agonists. Medical suppression decreases both breast cancer recurrence and mortality rate with 4% and 3% respectively (Baum et al., 2006; EBCTCG, 2005; Hackshaw et al., 2009).

A meta-analysis of data from almost 200,000 women collected over time in order to estimate the value of adjuvant radiotherapy, chemotherapy and endocrine therapy has been an important step in recognising the value of adjuvant therapy. The first results were published in 1988, and follow-up data are regularly published (Clarke et al., 2008; EBCTCG, 1988, 1992, 1998a, b, 2005). Meta-analyses have demonstrated that adjuvant chemotherapy reduces the relative yearly risk of death by almost 40% for women <50 years and by 20% for women 50-69 years old and that endocrine therapy with tamoxifen in oestrogen-receptor positive patients results in a more than 30% relative risk reduction of mortality (Clarke et al., 2008; EBCTCG, 2005).

The biological therapy trastuzumab entered breast cancer therapy in the late 1990s and has dramatically changed the outcome for women with HER2 over-expressing breast cancer. Trastuzumab is a monoclonal antibody that attaches to a growth-promoting protein known as HER2/neu which is present in larger than normal amounts on the surface of the breast cancer cells in about 15-20% of women with early breast cancer and 20-30% of women with advanced breast cancer. Trastuzumab can thus suppress HER2 stimulated tumour growth and may also activate the immune system to more effectively attack the cancer. In recent years, studies have shown that 1 year of adjuvant treatment with trastuzumab in women with HER2 positive breast cancer leads to a 50% reduced risk of recurrence, although the follow-up period of these patients is still limited (Piccart-Gebhart et al., 2005; Romond et al., 2005).

A recent update of the so called FinHer Trial, showed a value of adding only 9 weeks of trastuzumab concomitantly to adjuvant chemotherapy which calls for further research about the duration of adjuvant trastuzumab therapy (Joensuu et al., 2005).

Adjuvant chemotherapy is commonly given for a period of 4-5 months, followed by endocrine therapy for 3 years for hormone-sensitive patients. Some high risk patients may also be subject to prolonged endocrine treatment of up to 10 years. Trastuzumab is given in combination with or subsequent to adjuvant chemotherapy and is continued for a total period of 1 year. More clinical trials, for instance the so called SOLD-trial, have
been started with the concept of trastuzumab for a shorter period than one year according to the results of the FinHer trial.

Two other keys to the success in breast cancer treatment are evidence based treatment guidelines and multidisciplinary teams.

In Sweden there are both national and regional treatment guidelines based on, and regularly updated, in line with internationally accepted standards ensuring that treatment is modernized and of equal value irrespective of where the patient is living [Goldhirsch, 2009].

Breast cancer treatment for every patient is recommended by multidisciplinary teams where different specialists – surgeons, oncologists, radiologists, cytologists and pathologists – collaborate.

### 1.5.4 Prognostic factors

The definition of a prognostic factor is that it prognosticates the progression of untreated disease. Several prognostic factors are identified regarding breast cancer and constitute the basis in international and national guidelines for adjuvant treatment of breast cancer. However, more and better prognostic factors are needed to achieve more individualised therapeutic strategies that could generate improved survival of breast cancer.

**Stage**

The Tumour-Node-Metastasis (TNM) staging system is today the most important prognostic tool for breast cancer [Singletary, 2003]. The TNM system is based on primary tumour size (T), the presence of regional lymph node metastases (N) and distant metastasis (M) respectively. The 10-year overall survival reported in a retrospective study based on approximately 240 000 women with breast cancer showed relative survival as follows: Stage 0 patients 95%, Stage 1 patients 88%, Stage 2 patients 66%, Stage III patients 36%, Stage IV patients 7% (Bland et al., 1998).

T: Tumour size is another of the strongest prognostic factors in breast cancer (Koscielny et al., 2009). A tumour size of ≤ 5 mm is associated with a 100% 9-year distant disease free survival (DFS) (Joensuu et al., 2003). Patients with node negative breast cancers less than 2 cm, receiving no adjuvant therapy had a disease free survival (DFS) of 79%, while patients with primary tumours greater than 2 cm had a survival rate of 64% (Quiet et al., 1995).

N: The most important prognostic factor in breast cancer is however the axillary node status. The 10-year survival by disease stage

![Figure 6. 5-year survival by disease stage](image)
year recurrence rate for patients with node positive breast cancer is close to 70% while the corresponding rate for patients with node negative disease is 20-30% (Mirza et al., 2002). The risk increases with the number of affected nodes a diagnosis (fig 6).

**Histo-pathological grade**

The 3-grade system mostly used for breast cancer was presented in 1957 by Bloom and Richardson and was later modified by Elston and Ellis (Bloom and Richardson, 1957; Elston and Ellis, 1991). It is based on nuclear polymorphism, mitotic count and tubule formation. Histologic grade by Elston and Ellis has been demonstrated to be an independent prognostic value in some studies (Bloom and Richardson, 1957; Elston and Ellis, 1991; Kronqvist et al., 2002; Page et al., 1998). Grade 1 represents the least and grade 3 the most aggressive breast cancer cells. Patients with a grade 1 breast cancer have been reported to have a 95% 9-year survival (Joensuu et al., 2003).

1.5.5 Predictive factors

A predictive factor predicts the most likely therapy response to a certain therapeutic agent. Testing for biological markers provides a basis for the selection of some types of medical therapies (Bergh, 2009; Wennmalm et al., 2007).

**ER = estrogen receptor and PR = progesterone receptor**

The existence of ER and/or PR on the breast cancer cell surface makes the cells sensitive to stimulation with estrogen and progesterone. The stimulation results in cancer cell proliferation and cell growth. Thus ER and PR predicts response to endocrine treatment of breast cancer. Tamoxifen blocks the ER and prevents stimulation while aromatase inhibitors lowers the levels of estrogen in the blood and thus indirectly prevents stimulation.

**Proliferation**

Increased cell proliferation has in some, but not in all studies, demonstrated an association with a worse prognosis (Ferno et al., 2000; Stal et al., 1994).

A recent study showed that tumours with a cell proliferation rate of >20% (measured as Ki-67 positive cells where Ki-67 is a cell cycle specific antigen on the surface of proliferating cancer-cells) (Urruticoechea et al., 2005) had a worse 9-year DFS (distant free survival) of 80% compared to 90% for those with <20% positive cells (Joensuu et al., 2003). Proliferation rate has been correlated with chemotherapy sensitivity (Colleoni et al., 1999; Vincent-Salomon et al., 2004).

**HER 2 = Human Epidermal Growth Factor Receptor 2**

Breast cancer cells with a protein over expression and/or gene amplification of the oncogene HER 2 are associated with aggressive biological behaviour and reduced survival in both node negative and node positive breast cancers (Lohrisch and Piccart, 2001; Revillion et al., 1998; Stal et al., 2000). HER2 is used for selection of the about 20% of breast cancers patients sensitive for trastuzumab therapy (humanised
Trastuzumab is an important treatment in the adjuvant setting with a statistically significant reduction of the number of events (recurrence of breast cancer, contra lateral breast cancer, second non-breast malignant disease or death) in the trastuzumab and chemotherapy-treated patients with a 50% reduced risk of recurrence (HR 0.5 95% CI 0.4-0.7) (Dowsett et al., 2009; Piccart-Gebhart et al., 2005). International guidelines today recommend trastuzumab for 1 year after or in combination with adjuvant chemotherapy for HER2-positive patients.

1.5.6 The prize of progress

However, more and better prognostic and predictive factors are needed to achieve more individualised therapeutic strategies in the treatment of breast cancer in order to improve breast cancer survival and prevent side effects that are so far inevitable. The consequence today is over treatment of many patients as adjuvant treatments are recommended based on statistical risks of relapse according to different tumour characteristics (lymph metastases, tumour size, receptors for oestrogen and progesterone, gene amplification of HER2, proliferation rate) in combination with patients’ age and general state of health. Further refinement in the classification of breast cancer tumours and individualisation of treatment will most likely take place based on the present development in the fields of genomics and proteomics.

The “costs of cure” for patients include side effects of treatment, the most common including different types of climacteric symptoms due to chemotherapy and endocrine treatment which strongly influence quality of life. There is a strong need for more specific factors determining treatment on an individual basis. Extensive research efforts are concentrated on this issue - of outmost importance to patients and to society.

Other “costs of cure”, for patients and society involve direct costs (30%) for drugs, hospitalisation, outpatient visits, health-insurances and for indirect costs (70%) for productivity losses due to sick leave and preterm retirement (Lidgren et al., 2007).

Breast cancer survivors is an increasing and strong group of women whose attitudes to illness, treatment, quality of life and research needs a lot of further investigation.

1.6 INFORMATION NEEDS AND PATIENT PARTICIPATION IN TREATMENT DECISIONS

Breast cancer treatment of today involves several difficult choices for both patients and physicians. The number of treatment options increase over time and many patients are also offered to participate in clinical trials where benefits and risks may be uncertain. The amount of information given is often extensive. A prerequisite for participation in treatment decisions is a well-informed patient who is capable of having a dialogue with the medical staff.
There is an increasing public interest in patient’s rights, status and role in medical care. Guidelines in the Swedish Health and Medical Services Act are dated 1982 and framed only in broad general terms (1982). According to this document health care should:

- build on respect for the autonomy and integrity of the patient
- as far as possible be worked out and accomplished in cooperation with the patient
- give individually adjusted information to the patient about her/his state of health and about available methods for examination, care and treatment

The patient does not have the right to demand any specific therapy. All treatment must be evidence based or given in agreement with clinical experience. When different equivalent therapies are available the choice should be the one that the patient prefers, costs considered. Patients with a life threatening or very serious illness have the right to a second opinion.

Issues of patient involvement in treatment decisions are debated internationally. The resolution on breast cancer of the European Parliament (2002) states:

“Women diagnosed with breast cancer should from the responsible physician be given relevant information about diagnosis and treatment. Furthermore they should, after information about side effects, be involved in the choice of treatment” (Europaparlamentet, 2003).

The European Parliament also encourages member states to decide on legislation about patient’s individual rights.

This approach implies respect for patient’s autonomy in contrast to an old paternalistic system of health care where the physician made all the decisions for the patients. However, respect for the patient’s opinion also means respect for a more passive and inactive role.

Patient information in history

Current attitudes towards communication between patients and physicians certainly differ from those of ancient medicine when “white lies” about diagnosis and prognosis were common (Sokol, 2006). In the Hippocratic writings (400-500 BC) doctors were encouraged not to reveal anything of the patient’s future or present condition (Sokol, 2006). The primary task was to not hurt patients and to not destroy hope. Also Plato approved of doctors lies and draws an analogy between lies and medicines as treatment.

This view was to prevail through the centuries and was incorporated in the first Code of Ethics 1847 by the American Medical Association (AMA). Only if absolutely necessary doctors may share “gloomy prognostications” with the patient but they are recommended to inform friends and relatives. The emotional state of the patient was believed to affect the ability to fight the disease.
Quotation: “The life of a sick person can be shortened not only by the acts, but also by the words or manner of a physician. It is therefore a sacred duty to avoid all things which have a tendency to discourage the patient and to depress his spirits” (1847).

During the 20th century there has been a steady development towards increased openness and the supremacy of truth. The relationship between truth and loss of hope was questioned and patient’s ability to cope with bad news was emphasized. A doctor in Boston (Richard Cabot), wrote that “a lie saves a present pain at the expense of a future greater pain (Cabot, 1903; Dodds, 1993; Jackson, 2001).

A British author (Maurice Davidson) argued that doctors should disclose information even to severely ill patients as “a patient has a perfect right to demand reliable information about his condition (Davidson, 1957). His views were unusual in the 1950’s (Davidson, 1957).

One reason in earlier times for with-holding the truth might be the fact that there were no drugs with documented effect against different diseases. Thus, the placebo effect and a sense of confidence were most important (Sokol, 2006).

Gradually from the 1950’s effective drugs became available and started a change towards greater openness. In 1953 doctors in Philadelphia answered questions about information to patients with a cancer diagnosis (Fitts and Ravdin, 1953). 69 % answered that they did not inform and only 3 % that they always informed the patient. The most frequent reason for not telling the patient was “unfavourable emotional reaction”. The second most cited reason was a request from the patient’s family not to inform, reflecting a time when relatives often knew a diagnosis or prognosis before the patient. The concept of cancer as a “death sentence” was probably important in doctor’s reluctance to disclose a diagnosis. Three years before that publication another study reported that 89 out of 100 cancer patients wished to know their diagnosis (Kelly and Friesen, 1950).

In 1961, another study in the US reported that 90 % of doctors would not usually inform about a cancer diagnosis, many actively changed the diagnosis to avoid to mention cancer. (Oken, 1961). In response to the same questions 97% of American doctors in 1979 would disclose a diagnosis of cancer (Novack et al., 1979).

During the shift towards increased truth-telling the association between cancer and death was successively weakened by more effective treatment, and better public understanding. Still information about prognosis may be even more difficult than informing about the diagnosis. Doctors may emphasize treatment and withhold prognostic information (Christakis, 2001; Miyaji, 1993).

The change towards increased openness is far from universal and influenced by cultural, legal and economic differences. In many countries e.g. Lebanon, Singapore, China and Japan patients with cancer are often not told their diagnosis (Fan and Li, 2004; Hamadeh and Adib, 1998; Lee and Wu, 2002; Seo et al., 2000).
Patients information needs are strong

There is clear evidence that patients do want information (Blanchard et al., 1988; Cassileth et al., 1980a; Degner et al., 1989; Fallowfield et al., 1995; Strull et al., 1984; Sutherland et al., 1989) and that doctors tend to underestimate this need (Blanchard et al., 1988) (Degner et al., 1989; Strull et al., 1984). This was indicated already 25 years ago in patients with high blood pressure (Strull et al., 1984) and later confirmed in cancer patients (Blanchard et al., 1988; Degner et al., 1989; Fallowfield et al., 1995) (Fallowfield et al, 1995). Among European women only one third were content with the information given (Veronesi et al., 1999). The most common complaint was too little information and patients asked for more emotional support from their doctors.

Most patients want a maximum of detailed information (Cassileth et al., 1980a; Fallowfield et al., 1995; Meredith et al., 1996). An overwhelming majority (94%) of cancer patients wanted as much information as possible, good or bad (Fallowfield et al., 1995). Those who wanted less information were older or had a worse prognosis.

There is a documented need for disease specific information among cancer patients. When patients were to consider seven types of information i.e. name of the disease, cancer or not, development, chance of cure, possible treatments, side effects and how treatments worked more than 90 % answered to all seven alternatives either “I absolutely need that information” or “I would like that information” (Jenkins et al., 2001). Only 5 % wanted information only if it was good news and 8 % wanted the doctor to decide which information was to be given. As many as 98 % wanted to know if they had cancer or not and 95 % wanted to know what was the chance for cure.

An instrument based on a method of paired comparison has been developed by Degner et al (Bilodeau and Degner, 1996; Davidson, 1957; Degner et al., 1997) to study patients’ priorities among different information items. Data show the three most important items to be chance of cure, stage of disease and treatment options (Bilodeau and Degner, 1996; Davidson, 1957; Degner et al., 1997; Luker et al., 1995).

Patients’ recall is an important aspect of the information process. Only half of the information given in hospitals is remembered and about cancer only 25 % (Beck and Clark, 1988; Pickersgill and Owen, 1992). Threatening information and information given at the start of a consultation is best remembered. When many statements are given the recall is reduced (Ley, 1997). Patients’ knowledge about their body, health, illness and treatment is often poor (Boyle, 1970; Veronesi et al., 1999). Only 27 % of cancer patients were reported to understand all of the written materials available to them (Cooley et al., 1995).

The information process is not just about the desired amount of information but includes the total communication between the patient and care givers. Breaking “bad news” may be stressful for both parties. Physicians have a need for education and training (Blanchard et al., 1988; Girgis and Sanson-Fisher, 1995; Hopper and Fischbach, 1989; Ptcak and Eberhardt, 1996). Insufficient training in communication skills has been shown to contribute to stress and a lack of work satisfaction (Fallowfield and Jenkins, 1999). Physicians find it easy to identify with the patient and difficult to
handle agony and despair. Training in communication skills may improve patient’s ability to adjust to a cancer diagnosis and its treatment (Aspegren et al., 1996; Fallowfield, 1992; Fallowfield et al., 1998a; Ford et al., 1994; Maguire and Faulkner, 1988; Slevin et al., 1996).

1.7 PATIENT PARTICIPATION IN TREATMENT DECISIONS

In Sweden and many other countries commissions in healthcare are working to find strategies to strengthen patients’ rights, to improve patient information and stimulate patient participation in medical decisions. What role do patients want to have in treatment decisions?

When cancer patients were compared with healthy individuals, the majority (59%) of cancer patients preferred a passive role, whereas the majority (64%) of the general public thought they should be very active and even wanted to select their own treatment if they were to develop cancer (Degner and Sloan, 1992).

Not even half of Swedish patients (41%) waiting for surgery regarded the decision to operate as a joint patient–doctor decision Nevertheless as many as 73% felt that their involvement in the decision-making process was satisfactory. Cancer patients did not differ in this respect (Larsson et al., 1989). Reports from other countries suggest, however, that patients with cancer may prefer a more passive role (Beaver et al., 1996).

In a large European study of women diagnosed with female cancers, 44 % preferred to leave treatment decisions to their doctor Those more interested in participating in treatment decisions were younger than 60 years and better educated. Patients with recurrence of disease wanted more often to participate in treatment decisions (Veronesi et al., 1999). Likewise in Canadian studies some 30-50% of patients with prostate and breast cancer wanted a passive role in treatment decisions (Bilodeau and Degner, 1996; Davison et al., 1995; Degner et al., 1997).

In a study with breast cancer survivors in Canada patients chose their preferred patient role from five different patient roles with a varying degree of influence on treatment decisions (Fig 7 next page).

By convention role A+B are considered active, role is C collaborative or shared and D+E are passive (Degner et al., 1997).

Patients were also asked what role they actually had in treatment decisions (Degner et al., 1997). Only 42 % believed they had achieved their preferred level of control which is considered a striking discrepancy. Among the discontented patients more patients wanted to be more active than patients wanting to be more passive. A group of 15 % believed they had been pushed to more decisional control than they really wanted.
In a British study using the same instrument there was a strong preference for the two most passive roles with 52% preferring role D and E. Also here many patients were unsatisfied, only 39% achieved their preferred role in decision making, most of them wanting to have a more active role (Degner et al., 1997).

The decision making process regarding adjuvant therapy is very compressed, with final decisions about treatment being reported to be 82% of patients within the first clinic visit (Siminoff et al., 1989). The pressure to make decisions quickly may leave women feeling they have no choice but to follow the physicians’ recommendations (Degner et al., 1997).

Most data on decision making in breast cancer treatment deals with the type of surgery. Women seem to benefit from participation. When patients were encouraged to participate in the decision of breast-conserving therapy versus mastectomy they had a lower incidence of anxiety and depression than those whose surgeons made the decision (Fallowfield et al., 1990). In a follow-up study three years later, half of the patients had positive reactions to the fact that they had had a choice (Fallowfield et al., 1994). Some patients (24%) considered the decision very difficult—13% had not been able to reach a decision but had asked their physicians to decide on their behalf.

Research in the new field of decision-making will add facts and arguments to the ongoing ethical and political debate about patient’s rights. In the US and Canada, research in medical decision-making is established, mainly as a result of the ethical debate about informed consent (Cassileth et al., 1980b; Lantos, 1993). In Sweden, as well as in most European countries, this type of research is developing.
In agreement with Degner et al., we decided to apply their research design and tools regarding patients’ information needs and preferences for participation in treatment decisions on a cohort of breast cancer patients in Stockholm (Degner et al., 1997).

1.8 THE MEANING OF BREAST CANCER

The meaning that breast cancer patients attribute to their disease reflects psychological as well as cultural factors. The link between emotional factors and breast cancer has always been strong with associations to femininity, ideas of beauty, sexuality, fertility and motherhood.

In 200 AD the Greek philosopher-physician Galen stated that breast cancer was more often seen in melancholy than in sanguine women (Luker 1996). In the 19th century an English surgeon declared that grief and anxiety were the most frequent causes of breast cancer, others claimed that people got cancer as a result of hyperactivity (Sontag 1979). The possible impact of psychosocial factors as causes of cancer and on the prognosis of cancer has attracted a lot of attention (Greer 1979). A review reported that the ratio of studies finding no relationship between psychological responses and survival to those who did find some relationship was in the order of 1:3 (Watson & Ramirez 1991). There are several studies about the association between negative events of life and breast cancer. Results are unclear and contradictory (Duijts et al 2003.; Gerits 2000). A meta-analyses of reports from 1966-2002 did not show connections between negative events of life and an increased risk of breast cancer (Duijts et al. 2003) besides a weak association with the death of a husband. However, such a serious trauma as losing a child has not demonstrated an increased risk to develop breast cancer according to a Swedish study (Lambe et al. 2004). Another Swedish study did report an increased risk of breast cancer for women who had stressed a lot (RR 2.1), a result that needs to be confirmed in further research (Helgesson et al. 2003).

Today, the “meaning of illness” may also be influenced by political and public debate on e.g. consumer attitudes, patient information and participation in treatment decisions. Our ‘health culture’, encouraging fighting spirit and describing the immune system in military terms, presumably affects patients’ perceived meaning of illness and assumed patient roles. In modern Western society the dominant discourse surrounding cancer is also reported to be that of hope (Luptin 1994).

While illness is defined as the experience of disease, including feelings of changes in the body disease is a condition diagnosed by a doctor and related to pathological findings (Luker 1996).

A diagnosis of breast cancer is an event in life that strongly affects the woman. Several studies have identified how priorities in life may be reconsidered in response to a diagnosis of breast cancer (Carter 1993, Jensen 2000, Landmark 2001). Some report positive changes with increased appreciation of life, change of priorities, spiritual change, more close relationships to family and friends and a better self confidence (Kornblith & Ligibel 2003).
The meaning patients attribute to their illness may influence coping strategies and abilities. Coping is a multifaceted concept and the subject of a vast literature. Coping has been seen from a psychological perspective as developing strategies for dealing with threat with the emphasis on conflict and defences (Lazarus 1966). Others saw coping from a sociological point of view as a problem-solving behaviour emphasizing tasks to be performed and challenges to be met (Mechanic 1968). Active contra avoidant coping strategies have been described. (Carver 1989). Active coping implies a change in the nature of the stressor and how it is perceived. Avoidant strategies intend to avoid a direct confrontation with stressful events and have been identified as psychological risk factors or markers for adverse responses to stressful life events (Holahan 1987).

Data on the potential association between coping-strategy and prognosis are conflicting. Patients reacting with “fighting spirit” or “denial” (“positive avoidance”) had a better prognosis than those reacting with “helplessness” or with a fatalistic approach (Greer, Morris & Pettinggale 1979, Greer et al 1990, Pettinggale et al 1985). A review from 2000 concluded that there was an increased risk for patients reacting with helplessness/hopelessness (Gerits 2000) but these findings has also been questioned (Petticrew et al. 2002).

In 1970 Lipowski, a Canadian psychiatrist stated that patients’ perceived meaning of illness would influence their choice of coping strategies, which as he wrote might spell ‘the difference between optimum recovery and psychological invalidism’ (Lipowski 1970).

According to Lipowski, coping behaviour is a result of multiple factors—intrapersonal, disease-related and environmental.

Lipowski suggested eight meanings of illness: challenge, enemy, punishment, weakness, irreparable loss, relief, strategy and value. Challenge is the meaning leading to active and adaptive coping strategies and thus socially desired. Value – that illness and suffering have an intrinsic value – might be a way to develop and mature. Lipowski gave his interpretations of all eight categories (Table 2 next page). Lipowski’s thesis from 1970 has had an impact on the debate, particularly in Canada and the US, and on the development of the concept of coping.

In Europe, Antonovsky’s concept of a ‘Sense of Coherence’ has had more influence (Antonovsky 1987). According to Antonovsky, here the experience of health is related to a ‘Sense of Coherence’ in an individual, societal and cultural context. The ‘Sense of Coherence’ starts to grow during childhood and ‘represents a web of linkages between the person and her or his world’. Health represents a health continuum, the position varying with time and is thus not a condition of healthy or ill. This definition of health as a relative state, allows for health even in a situation of diagnosed disease. This can be related to Lipowski’s thesis that intrapersonal, disease-related and environmental factors have an influence on a patient’s subjective meaning of illness.
We sought to fulfil the research collaboration with Degner by testing Lipowski’s instrument on the Swedish breast cancer patients who took part in our decision-making study reported in paper I.

Table 2. Meaning of illness with abbreviated interpretations based on Lipowski.

<table>
<thead>
<tr>
<th>Category</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Challenge</td>
<td>The disease is perceived as any other task in life that can be mastered with means and resources available.</td>
</tr>
<tr>
<td>2. Enemy</td>
<td>The disease is perceived as an attack by hostile forces, internal or external.</td>
</tr>
<tr>
<td>3. Irreparable loss</td>
<td>The disease is perceived as an overwhelming loss that nothing can replace. For some individuals even a seemingly minor loss of function may do this.</td>
</tr>
<tr>
<td>4. Punishment</td>
<td>The disease is perceived as just or unjust. It can be regarded as a means for atonement, forgiveness.</td>
</tr>
<tr>
<td>5. Weakness</td>
<td>The disease is perceived as a failure, a sign of loss of control with negative moral implications. A feeling of shame may be involved.</td>
</tr>
<tr>
<td>6. Value</td>
<td>The suffering related to the disease is perceived as something valuable, as a way to develop and mature.</td>
</tr>
<tr>
<td>7. Relief</td>
<td>The disease is perceived as a respite from demands and responsibilities to be strong or a respite from a current crisis.</td>
</tr>
<tr>
<td>8. Strategy</td>
<td>The disease is perceived as a technique to secure attention, support or compliance from others.</td>
</tr>
</tbody>
</table>

1.9 HRT AND BREAST CANCER

Hormone replacement therapy (HRT) is and has been an important medical treatment for climacteric symptoms. During the 1980s and 1990s HRT was frequently prescribed to relieve women from night sweats, hot flashes and sleeping problems. Subsequently new data were presented reporting other positive health effects, including decreased risk of coronary heart disease, stroke, depression and osteoporosis (Falkeborn et al., 1992; Falkeborn et al., 1993; Grodstein and Stampfer, 1995; Kiel et al., 1987; Stampfer and Colditz, 1991).

The use of HRT was, however, questioned because of an increased risk of developing breast cancer (Bergkvist et al., 1989; Steinberg et al., 1991). Newly diagnosed breast cancer patients were thus recommended to stop HRT, as the hormones might stimulate breast cancer cells and increase the risk of recurrence.

Based on this uncertainty two randomized trials of HRT in breast cancer patients were started in Sweden, the HABITS trial (Hormonal replacement therapy After Breast cancer – Is It Safe?) (Holmberg and Anderson, 2004) and the Stockholm trial (von Schoultz and Rutqvist, 2005).

In both Swedish trials with HRT after breast cancer recruitment of patients was slower than expected and in 2002 there was an agreement to pool safety and final analyses in the two trials. In 2004, safety data from the HABITS-trial showed an increased risk of recurrence among HRT-users (Holmberg and Anderson, 2004). As a consequence, both
Swedish HRT trials were stopped prematurely by the Medical Products Agency. However, no increased risk of recurrence was reported in the treatment group of the Stockholm trial (von Schoultz and Rutqvist, 2005). The HABITS trial has been updated in 2008, showing a continued increase in breast cancer risk (Holmberg et al., 2008).

Furthermore, in 2002 the LIBERATE study (Livial Intervention following Breast cancer: Efficacy, Recurrence And Tolerability Endpoints trial) was started (Kenemans et al., 2009). This is a multicenter randomized placebo-controlled trial on tibolone which is a synthetic steroid with somewhat androgenic properties. Recruitment in the LIBERATE study was completed in 2004. Just recently, the study was stopped due to an increased risk of recurrence after a median of 3.1 years of follow up (Kenemans et al., 2009).

Numerous women all over the world are treated with different combinations of oestrogen and progestin for hormonal contraception and the alleviation of menopausal symptoms. Currently there is much confusion and an intense discussion about the long term safety of such hormone therapy. Randomized data have been published about the potential protective health effects vs. risks of HRT in healthy postmenopausal women (Beral, 2003; Chlebowski et al., 2003; Grady et al., 2002; Hulley et al., 1998; Rossouw et al., 2002). The expected protective effects against coronary heart disease and stroke were however not confirmed in an American randomized, primary prevention trial with more than 16 000 healthy postmenopausal women where health benefits were reported to be outweighed by risks (Chlebowski et al., 2003; Rossouw et al., 2002). In particular the effects on the breast have been focused. Following the release of the 2002 report of the Women’s Health initiative (WHI) trial of oestrogen plus progestin, the use of menopausal hormone therapy has decreased dramatically. As the incidence of breast cancer also dropped a cause-and-effect relation between hormone treatment and breast cancer was suggested but considered controversial. There could be other explanations such as a change in frequency of mammography.

In the present study we interviewed breast cancer patients during different phases of the Stockholm trial 1998-2003. The aim was to assess possible differences between participants and non participants. Also in a subgroup of participants health related quality of life effects of hormone therapy were explored.

1.10 PATIENTS IN RESEARCH AND CLINICAL TRIALS.

There has been a long and slow development towards the doctrine of informed consent in all research involving human beings. In 1721 prisoners at Newgate were offered free pardon if they agreed to be inoculated with infectious smallpox. Six condemned inmates, 3 men and 3 women, “volunteered”. They developed conspicuous local lesions but had little systemic disease and were dismissed from prison. The option if they did not “volunteer” was to be hanged! The question is raised by the author: “A stronger incentive to volunteer could hardly be imagined – but does this make the experiment unethical?” (Howard-Jones, 1982).
During the 18th century medical treatment was empirical but very frequent and prescriptions were described as “formidable compositions, a drug for every symptom and a few more for the pool” (Allbutt, 1921). Most experiments were performed by physicians upon themselves which at least guaranteed that they volunteered and were informed. In the first two decades of the 20th century the pharmaceutical revolution started with e.g. insulin, anaesthetics, analgesics, hypnotics, sedatives and treatment against infectious diseases. In Germany there was an intense debate in the 1920s and 30s about the uncontrollable use of new medicines and about unethical conduct. The medical profession was accused of “naked cynicism” and “worst form of charlatanism” (Stauder, 1931). In 1931 German guidelines were issued for innovative therapy and scientific experiments on man (1931) with recommendations for instance about that patients must give consent after unequivocal explanation and that risks must be weighed against benefits.

The disclosures at the Nurnberg trials of war crimes after World War II stimulated the development of the so called Nurnberg code of 1947, the code of ethics that was to direct all research where human beings were participating (Bergentz, 1997).

The code consists of ten articles dealing with the conditions for research where human beings participate:

- Voluntary participation is a definite prerequisite. The principal investigator is responsible for giving complete and correct information
- The research (project, experiment) must be expected to yield important results valuable to society
- The research must be based on animal experimentation and good knowledge about the disease
- The research must be carried out in a way that minimizes the risk of all kinds of injuries
- No research may be carried out in case of injury or death
- The risk of injury may never exceed the importance of the expected results
- Careful preparations and good equipment is demanded to minimize injuries
- The principal investigator must be scientifically well qualified
- The test subject must be able to discontinue (break) the research at any time
- The principal investigator is obliged to discontinue the research if there is a risk of injury of the test subject

The code was formulated by lawyers and was applicable on research with human beings without association to treatment, thus it was not primarily about patients. It was therefore criticized to be too “legal” without taking medical reality into account. The rigid demand for consent made research impossible in those who were under age, mentally disturbed and unconscious.

The Nurnberg code has played an important role in the development of research ethics and has been a basis of the so called Helsinki declaration, accepted in 1964 at a meeting in Helsinki with the general assembly of the World Medical Association. Up to now five revisions have been made, the latest at the meeting of the general assembly in Edinburgh in 2000 (Otte et al., 2005).
In the Helsinki declaration extended and precise writings are made in 32 items (Milton, 2002), about subjects uncapable of making a decision, demands for research protocols approved by an ethical committee etc. In item no 22 the demands on patient information are described in detail:

“In all kinds of research involving human beings every possible participant shall have enough information about the aim, the methods and the financing of the research, about possible conflicts of interest, affiliation of the researcher, expected advantages and possible risks as well as the side effects that the research might results in. The participant must be informed about the right to abstain from participation and about his or her right to discontinue participation at any time without being met with reprisals. After being assured that the participant has understood the information the physician must obtain his or her voluntarily given informed consent, preferable in writing. If written informed consent cannot be given, it must be documented and witnessed how the consent was given” (Bergentz, 1997).

The Helsinki declaration has later been the basis for the rules of Good Clinical Practice (GCP) regarding conduct of all clinical trials (Otte et al., 2005). The rules specify in detail what the patients must be informed about for insurance legal and ethical reasons. The amount and the degree of details of the information have then successively increased, the question is if it is for the benefit of the patients or just for legal reasons (Fallowfield and Jenkins, 1999). Thus, there is a debate about the informed consent process.

Difficulties in the information process

Patients offered participation in clinical trials thus receive a large amount of information that they cannot reject even if they do not want it. Many have questioned the ethics of overloading the patient with undesired information (Fallowfield and Jenkins, 1999). Patients who do not want all this information can only abstain from participating in clinical trials.

There is very little knowledge about the mechanisms to reach informed consent and if all the information given is applicable and meaningful to the patient (Sutherland et al., 1990).

There is evidence that the informed consent was not as informed as it should be (Montgomery et al., 1997) and reports revealed insufficient understanding by participating patients (Aaronson et al., 1996a; Brown et al., 2004; Hietanen et al., 2000; Jenkins et al., 1999). In one report many patients did not recall e.g. that they received experimental treatment (Sutherland et al., 1990). Either the information was inadequate, given in an incomprehensible way or it was not checked that the patient had understood (Fallowfield and Jenkins, 1999). To estimate the amount of information needed to be able to consider the consent as informed is reported to be particularly difficult (Tobias, 1998).
A recent report from the Clinical Trial Unit, CTU, at the Department of Clinical Oncology at the Karolinska University Hospital reveals that the majority of patients (33%; 92/282 with breast cancer) perceived themselves as well informed (Bergenmar et al., 2008). High levels of knowledge were found for some items e.g. over 90% responded correctly that the main reason for the trial was to improve treatment for future patients. However, only 24% responded correctly to the items stating “The treatment being researched in my clinical trial has been proven to be the best treatment for my cancer” and as few as 18% responded correctly to the item stating: “Compared to standard treatments for my type of cancer, my clinical trial does not carry any additional risks or discomforts”. Thus, patients overestimated the benefits and played down the risks associated with participation.

Breast cancer patients offered participation in clinical trials are almost always in a complex situation. In the adjuvant setting, information about clinical trials is often given directly after information about the cancer diagnosis or after surgery when a lot of other information is given that influence chance of cure and risk of recurrence. The next situation is at the time of systemic disease where the chance of cure often is no longer possible or when an ongoing treatment for metastatic disease has proved un-effective and the disease has worsened. Available treatment alternatives in this situation maybe a research project including increased uncertainty and demands for the patient.

Too few patients participate in clinical trials

According to several reports too few cancer patients participate in clinical trials, which delay research and the introduction of new drugs (Fallowfield and Jenkins, 1999; Slevin et al., 1995). There are several reasons for this including attitudes to clinical trials among physicians and patients (Fallowfield et al., 1994; Fallowfield et al., 1998b; Taylor et al., 1994).

The role of physicians

The reluctance of the physicians to offer patients trial participation is considered to be a greater problem than that of the patients (Fallowfield and Jenkins, 1999). Many physicians experience a conflict between their role as doctor and role as researcher. Others find it difficult to reveal uncertainty to the patient as it might influence the relation between the physician and the patient. Many report shortage of time to inform patients and deal with all the administration that clinical trials generate. They describe demands for handling a high number of patients, a daily lack of time in consultations and insufficient support to explain details in trials to obtain a well considered informed consent (Fallowfield and Jenkins, 1999). Lack of communication skills was reported as an important problem (Jenkins et al., 1999). To explain randomization, give complicated information about a trial and to reach an informed consent was reported by physicians as the worst problems (Fallowfield et al., 1998a). The conclusion in the report was that physicians, nurses and study coordinators need more education and understanding about patients’ attitudes and more communication training if the situation is to improve.
The role of patients

The most important reasons for patients to decline participation in trials are anxiety not to get the best treatment, anxiety about risk of randomization and a wish that the doctor selects a special treatment (Jenkins and Fallowfield, 2000) and fear of serious side effects (Jensen et al., 1993).

A British study reported on the other hand that patients were motivated to accept participation for the following reasons: their disease would be more carefully followed with different kinds of examinations, they would have a better chance to be treated by a doctor with a special interest in their disease, they would get more information about their disease (Slevin et al., 1996). Among 200 cancer patients more than 70% said they would accept participation in a randomized trial and the most important reasons were: others with the same disease could benefit from the results, the patients had a great confidence in their doctor, they thought that the study offered the best treatment available (Jenkins and Fallowfield, 2000).

“I had confidence in my doctor” was on the other hand reported as one of the most important reasons to decline participation in a randomized trial (Jenkins and Fallowfield, 2000). One reason might be a reflection of what the doctor giving the information seems to think. If the doctor seems enthusiastic or doubtful might thus be decisive even in the most regulated situation from an information point of view. The conclusion must be that communication as a whole is decisive.

1.11 HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Studies have shown that about 80% of women with breast cancer suffer emotional distress at the time of diagnosis and start of treatment (Spiegel, 1997). Fear of recurrence, agony of death and problems related to sexuality and work are most common (Spiegel, 1997) Generally anxiety and depression will then decrease during the first months after diagnosis (Brandberg et al., 2003; Peterson, 1996) when most patients have gone through surgery and adjuvant treatment has been started. There is a “plan for action” and the frequent contacts with health care makes it possible to discuss different problems. Quality of life seems to improve when stress is decreased during the first year after diagnosis (Brandberg et al., 2003; Schag et al., 1993; Shimozuma et al., 1999). Still as many as 20-30% of patients may have remaining problems up to two years after treatment (Irvine et al., 1991).

Factors associated with increased emotional stress are: previous psychical morbidity (Styra et al., 1993), high levels of emotional stress at the time of diagnosis and after surgery (Nordin et al., 2001; Schag et al., 1993; Shimozuma et al., 1999) and chemotherapy (Schag et al., 1993). Patients reporting optimism as well as younger patients have lower levels of psychic stress (Schag et al., 1993). Those with little social support and previous stressful life events seem to be especially vulnerable (Kornblith et al., 2001).

According to WHO, health was in the 50s defined as absence of disease and presence of physical, mental and social well-being (Velikova et al., 1999; WHO, 1958). A
number of questionnaires have been developed in order to evaluate Health-Related Quality of Life (HRQoL) in clinical trials as a complement to traditional end points (Aaronson et al., 1993; Cella et al., 1993; Coates et al., 1983; de Haes et al., 1990; Schag et al., 1991; Ware et al., 1990). The EORTC Quality of Life Group recommends the use of two types: one general, core questionnaire designed for cancer patients irrespective of diagnosis and one diagnostic-and/or treatment specific questionnaire (Aaronson et al., 1996b).

In early breast cancer no connection has been found between HRQoL and prognosis of disease (Efficace et al., 2004; Goodwin et al., 2004). In advanced breast cancer a positive association has been reported between prognosis and physical well-being, physical functioning, mood, social function and overall quality of life (Seidman et al., 1995).

Negative HRQoL consequences of adjuvant chemotherapy have been found to be transient and most studies report return to pre-treatment levels within one year after diagnosis (Ganz et al., 1998; Humy et al., 1996; Joly et al., 2000). In patients with stem cell/marrow-supported high dose chemotherapy (CTCb) or tailored FEC therapy there was a lower HRQoL at randomisation compared to healthy women and also a further decrease in HRQoL during treatment (Michelson, 2002). After one year most patients had recovered and the levels of functioning were higher than at randomisation. After two years decreased sexual enjoyment and an increase in hot flashes were reported compared to the values at randomization. Menopausal problems were not reported specifically except for hot flashes.

At the time of a breast cancer diagnosis, when women using menopausal hormone therapy (HRT) are told to stop the medication, many experience recurring menopausal symptoms as a result. Adjuvant treatment with chemotherapy and endocrine agents will further aggravate these symptoms (Fellowes et al., 2001; Nystedt et al., 2000). In pre-menopausal women, treatment with ovarian suppression and/or chemotherapy combined with endocrine treatment will result in premature menopause, often associated with more severe symptoms (Goodwin et al., 1999). Grave menopausal symptoms make many breast cancer patients consider stopping their endocrine therapy (Fellowes et al., 2001), despite being informed about the anti-tumoral effect of such treatment.

In healthy women HRT containing estrogen is currently the most effective treatment for menopausal symptoms, and may be used safely for at least four to five years without negative health effects (Utian et al., 2008). Some breast cancer patients with severe menopausal symptoms (Harris et al., 2002; Hickey et al., 2005b) coupled with the emotional distress associated with the cancer diagnosis, want to start their HRT treatment again. The therapeutic alternatives are few and have not been proven to have substantial effect (Hickey et al., 2005a).
2 AIMS

The aims of the present study were:

• to explore information needs among breast cancer survivors and their preferences for participation in treatment decisions

• to elucidate the meaning of illness among breast cancer patients

• to investigate attitudes among breast cancer patients towards clinical trials, benefits versus risks and the balance between quality and length of life

• to assess health related quality of life (HRQoL) in breast cancer survivors with and without HRT
3 PATIENTS, MATERIALS & METHODS

3.1 PATIENTS

A consecutive sample of 261 women (paper I and II) was taken from the attendance lists of the outpatient breast cancer clinic at the department of clinical oncology, Radiumhemmet, Karolinska Hospital in Stockholm. Eligible patients were diagnosed with breast cancer within the last 18 months treated with primary surgery and were less than 75 years old. The women were informed about the study by phone prior to the visit at the clinic and then received written and verbal information. 201 (paper I) and 187 (paper II) women respectively accepted participation. The study was approved by the ethics committee of the Karolinska Hospital.

The clinical material in paper III comprised 57 participants and 58 non participants in the prospective randomized Stockholm trial on HRT after breast cancer.

In paper IV a subgroup of 75 women from this trial was recruited for a study of health related quality of life. Out of these women 38 were randomized to HRT and 37 to the control group (fig. 8). Eligible women in the Stockholm trial were postmenopausal, primarily treated for breast cancer, free from recurrence, with or without menopausal symptoms and less than 75 years old. Ongoing adjuvant treatment was permitted (von Schoultz 2005). The studies were approved by the ethics committee of the Karolinska Institutet Nord.

3.2 INTERVENTIONS

Structured interviews (30-40 minutes) with patients in paper I and II were carried out on information needs (paper I), preferred/actual role in treatment decisions (paper I,II) and meaning of illness (paper II). Clinical data were collected from medical records.

A profile of information needs was established from the women’s ranking of nine different items/categories on e.g.: diagnostic stage, likelihood of cure, influence of treatment on social activities, physical and emotional impact, self care at home, physical and sexual attractiveness, benefits and risks of treatment, side effects and risk of relatives to develop the same disease. The questions were presented two at a time and the women had to choose the item in each pair that was of greatest importance. The
method of paired comparisons has been developed by Ross and Thurstone (Ross 1974, Thurstone 1974).

A card sort procedure (Degner 1992) was used to determine preferences for participation in treatment decisions (paper I, II). Five cards (A-E) described in words and pictures, different possible roles of patients in relation to their physicians (Fig. 7). The roles changed gradually from the patient selecting her own treatment (A) through a collaborative role (C) to the doctor selecting the treatment without involvement of the patient (E). The card sort procedure yields a ranking order of the five possible roles with the patient’s first preference at the beginning. Preference order was based on a scaling model (the “unfolding theory”) as developed by Coombs (Coombs, 1964). At the end each woman was asked also to select the card that best described the role she actually had in relation to her doctor when treatment decisions were made.

To establish the “meaning of illness” in the context of breast cancer (paper II) women were presented with eight cards each containing one of the categories defined by Lipowski (Lipowski, 1970). Based on individual choice the women were divided into three groups i.e. challenge, a “positive” (value/relief/strategy) or a “negative” (enemy/punishment/weakness/irreparable loss) meaning of illness. Data were also grouped and compared according to a classification used by Degner (Degner et al., 2003).

Patients in paper III were asked to complete five questionnaires: 1) comprised 9 items of information about HRT and breast cancer and were evaluated by a Likert scale as very important/important/less important/unimportant. In questionnaire 2) patients were asked to rank the importance of the 9 items using the method of paired comparison derived from Thurstone (Thurstone, 1974). This method has been used in several previous publications (Beaver et al., 1996; Degner et al., 1997) and in paper I. After basic information about clinical trials in general women were asked to complete a questionnaire 3) on 12 issues about participation in research, attitudes towards risk and quality versus length of life. Issues were evaluated by a Likert-scale. Questionnaire 4) was a Swedish translation of an instrument on patient’s attitudes to participation in clinical trials as previously used in a British study (Slevin et al., 1995). Patients valued 9 issues by a Likert-scale. The last questionnaire 5) comprised 5 cards describing in words and pictures the relation between patient – physician with a varying degree of patient participation in treatment decisions. The cards were the same as previously used in paper I and II and also by other groups (Beaver et al., 1996; Degner et al., 1997).

The health related quality of life for women in study IV was assessed at inclusion and at six and twelve months after randomization.

The EORTC QLQ-C30 is a HRQoL questionnaire (paper IV) for the measurement of quality of life in cancer patients in clinical trials (Aaronson et al., 1993). It consists of 30 items constituting five functional scales, nine symptom scales and one global quality of life scale. The validity and reliability of the Swedish version of this instrument has been previously reported and reference values for the general population
have been published (Bergman et al., 1992; Michelson et al., 2000; Sigurdardottir et al., 1996).

The EORTC QLQ breast cancer module, QLQ-BR23 (paper IV) comprises 23 questions and five multi-item scale to assess disease symptoms and side effects of treatment. The variables side effects, body image, sexual functioning and enjoyment were analyzed in the present study.

The Hospital Anxiety and Depression scale (HADS) (paper IV) is a brief self administered questionnaire to assess anxiety and depression among somatically ill non-psychiatric patients (Zigmond and Snaith, 1983). It consists of fourteen items and has shown good psychometric properties in a number of studies (Bjelland et al., 2002). A recent evaluation of the HADS in breast cancer patients found this instrument to be equally reliable as four weeks of daily registration of emotional distress (Arving et al., 2008).

3.3 STATISTICAL ANALYSES

Data on information needs (paper I, III) were analyzed using Thurstone scaling (Thurstone, 1974). Preference frequencies were divided by the number of patients and preferred proportions were translated into standard normal scores. Profiles of information needs were compared using a test for equality and after Bonferroni correction (Sloan et al., 1994). The Kendall coefficients of consistency and agreement were used to assess how consistent each participant was in her choices (Edwards, 1974). If not, inconsistencies in the form of circular triads occur. For example, if item 1 is preferred over item 2 by a participant, and item 2 over item 3, then item 1 would be preferred over item 3. If, instead, item 3 is preferred over item 1, a circular triad has occurred. The ranking order of preferred roles was calculated according to Coombs (Coombs, 1964) (paper I). Information needs profile analyses were also performed according to Sloan et al (paper I, III) (Degner et al., 1997; Sloan et al., 1994).

The Students t-test (III) and Chi-square analyses (paper I-III) were used to investigate possible differences in distribution between groups and patients preferred and actual role regarding participation in treatment decisions. Congruence between preferred and actual role was also assessed by the Wilcoxon Signed Rank test (paper III).

Differences between different treatment regimens (paper IV) were analyzed by factorial ANOVA or by t-test for unpaired samples. Changes over time were analyzed by ANOVA for repeated measures. Correlations were assessed using Spearman’s rank test.

Levels of significance were set at p<0.05.
4 RESULTS

4.1 PAPER I

Sample

201 patients were interviewed, 83 of them 1-6 months after breast cancer diagnosis and 118 patients 6-18 months after diagnosis.

Information needs

Patients valued nine items of information (Table 3). The possibility of cure was ranked highest of the information needs, with information about stage of disease and type of treatment as second and third priorities (fig 9, next page). Information related to social consequences of cancer, self-care, how family and friends may be affected and sexual attractiveness was rated much lower.

The Thurstone scale scores for the two top priorities (cure, stage of disease) were significantly different from all four items rated lowest (pairwise tests correlated for multiple comparisons by use of the Bonferroni correction, p-value=0.001). There was also a strong suggestion that the third priority (treatment options) belonged to the group of top ranked information needs (p-value=0.01).

The preferred role of the patient and time from diagnosis did not change her ranking of the three items of information on top compared to the whole sample. In relation to age and education, the same three items of information were given priority, with only one exception: women with intermediate levels of education, rated information about treatment options as second and stage of disease as third priority. Young women (≤ 50 years) rated information about sexual attractiveness somewhat higher than older women (p=0.005).

<table>
<thead>
<tr>
<th>Table 3. Information needs about breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nine items of information</td>
</tr>
<tr>
<td>1. Information about the diagnostic stage and the extent of involvement of my disease.</td>
</tr>
<tr>
<td>2. Information about the likelihood of cure from my disease.</td>
</tr>
<tr>
<td>3. Information about how the treatment may affect my ability to carry on my usual social activities (sports, hobbies, etc).</td>
</tr>
<tr>
<td>4. Information about how to handle the physical and emotional impact of the disease on my family and significant others.</td>
</tr>
<tr>
<td>5. Information about caring for myself at home (nutrition, support groups, home care, social workers, mental health workers, etc).</td>
</tr>
<tr>
<td>6. Information about how the treatment may affect my usual feelings of physical and sexual attractiveness (breast disfigurement, breast prothesis, reconstructive surgery).</td>
</tr>
<tr>
<td>7. Information about different types of treatments (surgical, chemo-therapy, radiotherapy) and the possible benefits and risks associated with each treatment.</td>
</tr>
<tr>
<td>8. Information about how at risk my children and/or other family members are in developing the disease.</td>
</tr>
<tr>
<td>9. Information about possible unpleasant side effects of treatment (nausea, pain, change in physical appearance)</td>
</tr>
</tbody>
</table>
The Kendall coefficient of consistency showed a mean value of 0.988, indicating very high consistency. Participants in the study generally had few triads and 46 participants had no triad.

Maximum number of triads, 20, involved the combination of items 3, 5 and 8 and 17 triads involved the combination 3, 5 and 7 and 3, 5 and 9, respectively (Table 4). A small group of 11 patients was responsible for a mean of 17 triads, compared to a mean of 3.6 triads for the whole sample. The Kendall coefficient of agreement was 0.2999, indicating agreement among all women concerning overall priorities for information. Two different reliability tests were performed: The Gulliksen and the Tukey measures of 0.95 are close to maximal reliability.

*Patient roles (Preferred and actual role in treatment decisions)*

Regarding patients’ first preference, the most frequently chosen alternative was D (Fig 7 page 17, Table 4 next page). This alternative being the most passive of the three collaborative patient roles (B, C, D) was preferred by 56% of the patients. The majority of women (87%) preferred to be collaborative in treatment decisions to some degree (B+C+D). In the youngest age group (≤50 years), 96% of the patients preferred one of the collaborative roles.

The most active role (A) was preferred by 3% of all patients and 13% preferred to be on the active end of the scale (A+B), whereas 66% preferred to be on the passive end of the scale (D+E). This was most pronounced in the oldest age group (≥66 years), where 78% of the women were on the passive end of the scale (D+E). This group chose the most passive alternative (E) more frequently (23%) than younger patients (2% and 12% respectively. Women with high level of education preferred a more active role, e.g. 22% preferred a role on the active end of the scale (A+B) compared with patients with intermediate and low education (6% and 8%,) (Table 4, next page).
Table 4. Preferred role in treatment decisions

When asked about the role they actually had in treatment decisions, most of the patients (53%) reported the alternative D. The oldest patients reported having had the most passive role (E) to a greater extent (35%) than patients in both age groups under 66 years of age (9% and 21%, respectively).

Most of the patients played the role that they preferred in treatment decisions, 72% reported agreement with their first preference (Figure 10). About 20% of patients wanted to be more active and 8% more passive, whereas among the oldest patients (≥ 66 years) 13% wanted to be more passive.

Unfolding analysis

The unfolding theory is a tool to investigate the possible existence of an underlying dominant psychological dimension onto which each individual’s preference order can be placed. The results are illustrated graphically in Figure 11 next page. The preference orders that did agree with the model are above the horizontal line (49%) and the ones that did not agree are below the line (51%). To illustrate this graphically, the horizontal line was placed at zero, which means that negative values in reality are positive values.
The preferences of the patients did not agree with the proposed underlying psychological dimension of keeping-sharing-giving away control (ABCDE–EDCBA) according to the criteria postulated by Coombs (Coombs, 1964). DCBEA, which was the most frequently occurring single preference order (27%), did not fit with the proposed dimension. It starts with the combination DCB, which describes varying degrees of patient–doctor collaboration in treatment decisions. The same can be said about other preference orders that do not fit the model (BCDEA, BDCAE, BDCEA, CBDEA, DBCEA, DCBAE) but also about several that do fit (BCDAE, CBDAE, CDBAE, CDBEA). Together, these 11 preference orders of collaboration represented 66% (133 out of 201) of all preference orders, which constitutes a clear majority of patients’ choices.

4.2 PAPER II

Meaning of illness

Most of the patients chose challenge (33%) as their perceived meaning of illness (Table 5). Their second choice was enemy (22%) and third choice irreparable loss (15.5%).

The eight different meanings of illness were classified into three groups (Table 6 and 7). Chi-square analyses of subgroups showed that patients’ age had an impact – challenge was chosen by significantly more patients in middle life (51-65 years, 40%) and by fewer patients in the oldest age group (≥ 66 years, 17%) (p=0.014) (Table 7). Relief, strategy and value were chosen by more patients over 66 years (29%) than by patients in youngest and middle-age groups (11% and 7%), (p=0.014).
Table 5. Meaning of illness with abbreviated interpretations based on Lipowski. Results for 187 breast cancer patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Interpretation</th>
<th>No. (%) n=187</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Challenge</td>
<td>The disease is perceived as any other task in life that can be mastered with means and resources available.</td>
<td>62 (33%)</td>
</tr>
<tr>
<td>2. Enemy</td>
<td>The disease is perceived as an attack by hostile forces, internal or external.</td>
<td>42 (22%)</td>
</tr>
<tr>
<td>3. Irreparable loss</td>
<td>The disease is perceived as an overwhelming loss that nothing can replace. For some individuals even a seemingly minor loss of function may do this.</td>
<td>29 (15.5%)</td>
</tr>
<tr>
<td>4. Punishment</td>
<td>The disease is perceived as just or unjust. It can be regarded as a means for atonement, forgiveness.</td>
<td>16 (8.6%)</td>
</tr>
<tr>
<td>5. Weakness</td>
<td>The disease is perceived as a failure, a sign of loss of control with negative moral implications. A feeling of shame may be involved.</td>
<td>14 (7.5%)</td>
</tr>
<tr>
<td>6. Value</td>
<td>The suffering related to the disease is perceived as something valuable, as a way to develop and mature.</td>
<td>14 (7.5%)</td>
</tr>
<tr>
<td>7. Relief</td>
<td>The disease is perceived as a respite from demands and responsibilities to be strong or a respite from a current crisis.</td>
<td>7 (3.7%)</td>
</tr>
<tr>
<td>8. Strategy</td>
<td>The disease is perceived as a technique to secure attention, support or compliance from others.</td>
<td>3 (1.6%)</td>
</tr>
</tbody>
</table>

Table 6. Two groupings of categories regarding meaning of illness according to text

<table>
<thead>
<tr>
<th>Group of categories</th>
<th>No. (%) n=187</th>
<th>Group of categories according to Dognen</th>
<th>No. (%) n=177</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Challenge</td>
<td>62 (33%)</td>
<td>1. Challenge</td>
<td>62 (33%)</td>
</tr>
<tr>
<td>2. Enemy/Punishment/Weakness/Irreparable loss</td>
<td>101 (54%)</td>
<td>2. Enemy/Punishment/Weakness/Irreparable loss</td>
<td>101 (57%)</td>
</tr>
<tr>
<td>3. Value/Relief/Strategy</td>
<td>24 (13%)</td>
<td>3. Value</td>
<td>14 (8%)</td>
</tr>
</tbody>
</table>

Table 7. Differences in categories of meaning by age, stage of disease and preferred patient roles in decision-making

<table>
<thead>
<tr>
<th>Group of categories</th>
<th>No. (%) n=187</th>
<th>Age</th>
<th>Stage</th>
<th>Stage</th>
<th>Stage</th>
<th>Pat.</th>
<th>Pat.</th>
<th>Pat.</th>
<th>Pat.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=187</td>
<td>50+</td>
<td>diag.</td>
<td>interview</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Challenge</td>
<td>62 (33%)</td>
<td>28 (52%)</td>
<td>6 (17%)</td>
<td>4 (29%)</td>
<td>1 (25%)</td>
<td>8 (32%)</td>
<td>18 (44%)</td>
<td>32 (31%)</td>
<td>5 (26%)</td>
</tr>
<tr>
<td>2. Enemy/Punishment/Weakness/Irreparable loss</td>
<td>101 (54%)</td>
<td>65 (35%)</td>
<td>19 (54%)</td>
<td>6 (19%)</td>
<td>2 (75%)</td>
<td>11 (38%)</td>
<td>16 (29%)</td>
<td>68 (58%)</td>
<td>11 (58%)</td>
</tr>
<tr>
<td>3. Value/Relief/Strategy</td>
<td>24 (13%)</td>
<td>65 (7)</td>
<td>10 (29%)</td>
<td>9 (0%)</td>
<td>0 (0%)</td>
<td>2 (19%)</td>
<td>7 (17%)</td>
<td>12 (11%)</td>
<td>3 (16%)</td>
</tr>
</tbody>
</table>
Meaning of illness was also affected by stage of disease (Table 7). All six patients with distant metastases at the time of diagnosis chose enemy, punishment, weakness or irreparable loss as their meaning of illness. Of the 14 patients with metastatic disease at the time of interview, 10 patients chose enemy, punishment, weakness or irreparable loss and 4 patients chose challenge.

Highest priority was given to the same three information needs, and in the same order, in all three groups in Table 7 regarding meaning of illness as for all patients in paper I – i.e. chances of cure, stage of disease and different types of treatment. The distribution for meaning of illness by preferred patient roles is presented in Table 7.

We also analyzed our data with the same grouping as that reported by Degner et al. (Table 6). Two analyses of subgroups led to statistically significant differences only for different age groups (p=0.009). Patients in middle life (51–65 years) chose challenge more often (42%) and patients older than 65 years more seldom (19%) than all patients (35%). Patients in the oldest age group (22%) chose value more frequently than younger patients. There were no statistically significant differences in meaning of illness by other subgroups (education, stage of disease, time from diagnosis) or by information needs, or preferred and actual role in treatment decisions.

**Patients' subjective interpretations of their selected meaning of illness**

In the study population, 120 patients (64%) were able to explain -in their own words- how they interpreted the meaning of illness that they had chosen. Patients who chose challenge interpreted the word as: “the disease must be managed”, “a challenge to get well” and “something you have to go through”. Enemy was explained in words such as: “something that threatens me”, “something bad in my body that frightens me”, “strange, uncontrollable, inconceivable” and “poisonous, unfamiliar”. Irreparable loss was described as “something that cannot be repaired”, “life is lost”, “loss of health”, “loss of security” but also as “loss of a part of the body that means a great deal”. Punishment was interpreted as: “I have been a smoker”, “what have I done that gave me this!” and “I often joke that I have committed so many sins that now I am getting my punishment”. Weakness: “physical weakness”, “I have never felt strong and confident in myself” and “it is in the upbringing – you are weak if you are ill”. Value was interpreted as a “help to mature”, “experience”, “I do not take everything for granted, material things are not so important” and “I think differently and appreciate small things”.

None of the four patients that chose relief interpreted it in the same way as Lipowski (Table 5). The patients said: “a relief when I was told what it was”, “a relief that I did not need radiotherapy”, “a relief to get rid of it as it was cancer in situ” and “a relief that it is over”. Neither of the two patients who chose strategy interpreted it in Lipowskis terms (Table 5): The patients said: “you have to reconsider, it means changes, consider how to handle the situation” and “close to challenge” compared to Lipowsky: “the disease is perceived as a technique to secure attention, support or compliance from others”.

36
4.3 PAPER III

Women who accepted to join the clinical trial were older (p≤0.001) than those who did not (Table 8). More time had elapsed since their breast cancer diagnosis (p=0.018) and more patients used HRT at breast cancer diagnosis (p=0.005). In the participant group, fewer patients had stage 2 disease (p=0.005), they also had smaller tumours (p= 0.012); more patients had had breast conserving surgery (p=0.002) and fewer had been treated with adjuvant chemotherapy (0.020). However, there were no differences in adjuvant endocrine treatment (p=0.687) or in education level among participants and non-participants.

Table 8. Sociodemographic and disease data. Information from patients and their medical records. Data are given as mean (standard deviation) or percentage

<table>
<thead>
<tr>
<th>Variables</th>
<th>Participants (n=57)</th>
<th>Non-participants (n=58)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at interview (years)</td>
<td>60.7 (6.3)</td>
<td>55.3 (4.6)</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Time from diagnosis (years)</td>
<td>5.7 (4.34)</td>
<td>3.8 (3.77)</td>
<td>0.018**</td>
</tr>
<tr>
<td>HRT at diagnosis (yes/no)</td>
<td>73.7%</td>
<td>48.3%</td>
<td>0.005**</td>
</tr>
<tr>
<td>Lymph node metastasis (yes/no)</td>
<td>15.8%</td>
<td>40% (n = 48)</td>
<td>0.005**</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>14.1 (6.7) (n = 54)</td>
<td>20.0 (15.6) (n = 48)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Breast conserving surgery (yes/no)</td>
<td>78.9%</td>
<td>51.0% (n = 51)</td>
<td>0.002**</td>
</tr>
<tr>
<td>Adjuvant chemotherapy (yes/no)</td>
<td>17.9% (n = 56)</td>
<td>38.0% (n = 50)</td>
<td>0.020*</td>
</tr>
<tr>
<td>Adjuvant endocrine treatment (yes/no)</td>
<td>64.3% (n = 56)</td>
<td>68.0% (n = 50)</td>
<td>0.687</td>
</tr>
</tbody>
</table>

Statistically significant differences * p≤0.05; ** p≤0.01; *** p≤0.001.

4.3.1 Information needs

Questionnaire 1

Table 9, next page.

Most items of information were considered ‘very important’ by both groups. Only item 6, ‘information about how oestrogen therapy can affect physical health’ showed a difference between participants and non-participants. More participants (85.5 %) than non-participants (69 %) valued the item as ‘very important’ (p=0.045).

Questionnaire 2. Information needs profile (Fig 12 and 13)

Item 3, 2 and 1 were the three top priorities among both participants and non-participants but not in the same order. Item 3: ‘Information about the risk of recurrence of breast cancer with and without oestrogen therapy’ was ranked highest both by participants and non-participants.
Table 9. Information needs regarding HRT (estrogen) and breast cancer: Questionnaire 1. 
The patients were asked: How important is this information when you are asked about participation in the Stockholm trial? The alternative answers were: very important/important/less important/not important.

<table>
<thead>
<tr>
<th>Item of information</th>
<th>Participants (n = 33)</th>
<th>Non-participants (n = 58)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Information about the reason for not recommending estrogen therapy to breast cancer patients</td>
<td>85.5</td>
<td>81.0</td>
<td>0.619</td>
</tr>
<tr>
<td>2. Information about new research data about estrogen therapy and breast cancer</td>
<td>89.1</td>
<td>84.5</td>
<td>0.583</td>
</tr>
<tr>
<td>3. Information about the risk of recurrence of breast cancer with and without estrogen</td>
<td>92.7</td>
<td>91.4</td>
<td>1.0</td>
</tr>
<tr>
<td>4. Information about how recurrence in breast cancer is treated</td>
<td>79.6</td>
<td>84.5</td>
<td>0.623</td>
</tr>
<tr>
<td>5. Information about how estrogen therapy can affect menopausal symptoms</td>
<td>67.3</td>
<td>56.9</td>
<td>0.333</td>
</tr>
<tr>
<td>6. Information about how estrogen therapy can affect physical health</td>
<td>85.5</td>
<td>65.0</td>
<td>0.045*</td>
</tr>
<tr>
<td>7. Information about how estrogen therapy can affect sex life</td>
<td>54.5</td>
<td>43.1</td>
<td>0.261</td>
</tr>
<tr>
<td>8. Information about how estrogen can affect mental wellbeing</td>
<td>76.4</td>
<td>67.2</td>
<td>0.304</td>
</tr>
<tr>
<td>9. Information about side-effects of estrogen therapy</td>
<td>80.0</td>
<td>81.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Statistically significant differences: *, p ≤ 0.05

0.635 —— Risk of recurrence (3) —— 0.871 —— Risk of recurrence (3)
0.485 —— New research (2) —— 0.365 —— Net estrogen and breast cancer (1)
0.415 —— Not estrogen and breast cancer (1) —— 0.315 —— Treatment of recurrence (4)

0.063 —— Treatment of recurrence (4) —— 0.02 —— Side-effects (9)
0.111 —— Health effects (6) —— 0.177 —— Health effects (6)
0.134 —— Side-effects (9) —— 0.412 —— Mental well-being (8)
0.162 —— Mental well-being (8) —— 0.689 —— Climacteric symptoms (5)

-0.409 —— Climacteric symptoms (5) —— -0.904 —— Sex life (7)

-0.783 —— Sex life (7) —— -0.809 —— Climacteric symptoms (5)

Figure 12. Information needs profile for participants in the Stockholm trial. Patients’ ranking of nine items of information.

Figure 13. Information needs profile for non-participants in the Stockholm trial. Patients’ ranking of nine items of information.
The second and third item study patients had to chose from were ‘Information about new research data about oestrogen therapy and breast cancer’ (item 2) and ‘Information about the reason for not recommending oestrogen therapy to breast cancer patients’ (item 1). Participants ranked the two items in this order and non-participants ranked them in the opposite order. Item 7: ‘Information about how oestrogen can affect sex life’ was ranked lowest by both groups.

4.3.2 Patient participation in research and clinical trials

Questionnaire 3 developed at the Department of Clinical Oncology.

Table 10: Patients’ attitudes to participation in clinical trials. Questionnaire 3. The patients were asked: To what extent do you agree to the following statement? The alternative answers were: ‘I agree completely/to a great extent/to some extent/not at all.’

<table>
<thead>
<tr>
<th>Statement</th>
<th>% who chose ‘I agree completely’ or ‘I agree to a great extent’</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants</td>
</tr>
<tr>
<td>1. I think that research involving patients is important</td>
<td>91.1 (n = 56)</td>
</tr>
<tr>
<td>2. I think that research involving patients should be pursued even if one group of patients will not get the treatment that proves to be the best</td>
<td>39.6</td>
</tr>
<tr>
<td>3. I believe that research favours doctors more than patients</td>
<td>17.5</td>
</tr>
<tr>
<td>4. I am prepared to participate in a research project only if it can prolong my own life</td>
<td>26.4 (n = 53)</td>
</tr>
<tr>
<td>5. I am prepared to participate in a research project when it is unknown which treatment is best</td>
<td>71.4 (n = 56)</td>
</tr>
<tr>
<td>6. I am prepared to participate in a research project aiming at improving treatment for future patients, even if it does not improve my own chances</td>
<td>70.2</td>
</tr>
<tr>
<td>7. I want to live as long as possible - that is more important than having a good quality of life</td>
<td>10.5</td>
</tr>
<tr>
<td>8. I want to have a good quality of life - that is more important than having a long life</td>
<td>87.5 (n = 56)</td>
</tr>
<tr>
<td>9. I want doctors to discuss the effect on body prognosis and quality of life, when decisions are made about my treatment</td>
<td>100.0</td>
</tr>
<tr>
<td>10. I am prepared to receive treatment that improves my quality of life and my health in other respects even if the risk increases of a relapse in breast cancer</td>
<td>64.3 (n = 56)</td>
</tr>
<tr>
<td>11. I am not prepared to do anything that increases the risk of a relapse in breast cancer even if it improves my quality of life and health in other respects</td>
<td>27.3 (n = 53)</td>
</tr>
<tr>
<td>12. I regard life as full of risks you have to take if you want a good quality of life – this also includes the risk of a relapse in breast cancer</td>
<td>75.0 (n = 56)</td>
</tr>
</tbody>
</table>

Statistically significant differences: *, p ≤ 0.05; **, p ≤ 0.01; ***, p ≤ 0.001

Differences were analyzed between participants and non-participants who answered I agree completely or I agree to a great deal compared to those who answered I agree to some extent or I do not agree at all. Patients valued 12 statements.
There was a difference between participants and non-participants in attitudes to clinical trial participation. More participants than non-participants chose the alternatives: I agree completely or I agree to a great extent for statement 5 (p=0.002), 6 (p=0.014), 10 (p=0.001) and 12 (p=0.001). Table 10.

Patients did not agree to statement 7: ‘I want to live as long as possible – that is more important than having a good life’. 52.5 % of participants and 35.7 % of non-participants chose the alternative I do not agree at all (data not shown).

**Questionnaire 4 developed by Slevin**

The alternative answers were: ‘It attracts me a lot/fairly much/to some extent/not at all’

<table>
<thead>
<tr>
<th>Statement</th>
<th>% who chose 'It attracts me a lot' or 'It attracts me fairly much'</th>
<th>Participants in the Stockholm trial (n = 54)</th>
<th>Non-participants in the Stockholm trial (n = 58)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. … that my treatment is decided by lottery and not by my doctor</td>
<td></td>
<td>40.4</td>
<td>20.7</td>
<td>0.037</td>
</tr>
<tr>
<td>2. … that I contribute to knowledge and do mankind a service</td>
<td></td>
<td>90.7</td>
<td>65.3</td>
<td>0.001***</td>
</tr>
<tr>
<td>3. … that I get a better chance to be treated by doctors with a special interest in my kind of cancer</td>
<td></td>
<td>94.3</td>
<td>85.5</td>
<td>0.129</td>
</tr>
<tr>
<td>4. … that I have a better chance to get new treatments</td>
<td></td>
<td>98.1</td>
<td>75.9</td>
<td>0.001***</td>
</tr>
<tr>
<td>5. … that my treatment is decided by a panel of experts instead of by my doctor</td>
<td></td>
<td>75.5</td>
<td>46.6</td>
<td>0.002**</td>
</tr>
<tr>
<td>6. … that the course of my disease is more carefully followed with tests, examinations and check-ups by my doctor</td>
<td></td>
<td>92.6</td>
<td>86.2</td>
<td>0.364</td>
</tr>
<tr>
<td>7. … that I probably get more information about my disease</td>
<td></td>
<td>92.6</td>
<td>87.9</td>
<td>0.531</td>
</tr>
<tr>
<td>8. … that I have a better chance to get experimental treatments</td>
<td></td>
<td>83.0</td>
<td>58.6</td>
<td>0.007**</td>
</tr>
<tr>
<td>9. … that I do not choose treatment myself</td>
<td></td>
<td>45.3</td>
<td>34.5</td>
<td>0.332</td>
</tr>
</tbody>
</table>

Statistically significant differences: *, p ≤ 0.05; **, p ≤ 0.01; ***, p ≤ 0.001

We analysed differences between participants and non-participants who answered It attracts me a lot or It attracts me fairly much compared to those who answered It attracts me to some extent or It does not attract me at all. Patients valued 9 statements.

There were differences between attitudes among participants and non-participants. More participants answered It attracts me a lot or It attracts me fairly much to statements number 1 (p=0.037), 2 (p=0.001), 4 (p=0.001), 5 (p=0.002) and 8 (p=0.007). Table 11.
4.3.3 Patient roles

Questionnaire 5.

Most patients preferred a role of collaboration with their physician. As shown in table 12, the patient role C, ‘I prefer that my doctor and I share responsibility for deciding which treatment is best for me’, was preferred by 67.6 % of all patients, by 72.5 % of participants versus 63.0 % of non-participants. Only 1.9 % of all patients preferred role E ‘to leave all decisions regarding my treatment to my doctor’ but when asked what role patients experience in relation to their physician (actual role), as many as 15.7 % of all patients answered E. Some patients experienced role A (‘I prefer to make the final decision about which treatment I will receive’) as their actual role (2.9% of all patients) while 0 % chose A as their preferred role, meaning they wanted to take on all responsibility for treatment decisions.

Figure 7. Five different patient roles in treatment decisions

Table 12. Patient roles. Questionnaire 5. Each patient selected her preferred role and her actual role in treatment decisions. Data are given as percentages

<table>
<thead>
<tr>
<th>Patient role</th>
<th>All patients</th>
<th>Participants</th>
<th>Non-participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferred</td>
<td>Actual</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>(n = 105)</td>
<td>(n = 102)</td>
<td>(n = 51)</td>
</tr>
<tr>
<td>A... to make the final decision about which treatment I will receive</td>
<td>0</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td>B... to make the final decision about my treatment after seriously considering my doctor’s opinion</td>
<td>9.5</td>
<td>11.8</td>
<td>7.8</td>
</tr>
<tr>
<td>C... that my doctor and I share responsibility for deciding which treatment is best for me</td>
<td>67.6</td>
<td>48.1</td>
<td>72.5</td>
</tr>
<tr>
<td>D... that my doctor makes the final decision about which treatment will be used, but seriously considers my opinion</td>
<td>21.0</td>
<td>24.5</td>
<td>19.6</td>
</tr>
<tr>
<td>E... to leave all decisions regarding my treatment to my doctor</td>
<td>1.9</td>
<td>15.7</td>
<td>0</td>
</tr>
</tbody>
</table>
As illustrated in Table 13 significantly more women in both groups wanted to be more active (26) compared to those who want to be more passive (7) (p=0.007). This was also true among participants with 17 patients wanting to be more active and 1 patient more passive (p=0.001), but not among non-participants. Most patients, 66%, had the role they preferred in treatment decisions and reported agreement regarding preferred role and actual role.

4.4 PAPER IV

No statistically significant differences were present at baseline between women in the HRT group and those without such treatment (the Control group) with respect to HRQoL, anxiety or depression. The results for women with data from all three points of assessment are given in Tables 14 and 15.

Table 13. Patient roles. Congruence between patients’ preferred and actual roles. (All patients in the study did not choose both their preferred and actual roles)

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Agreement</th>
<th>More active</th>
<th>More passive</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>98</td>
<td>65</td>
<td>26</td>
<td>7</td>
<td>0.007**</td>
</tr>
<tr>
<td>Participants</td>
<td>45</td>
<td>27</td>
<td>17</td>
<td>1</td>
<td>≤0.001***</td>
</tr>
<tr>
<td>Non-participants</td>
<td>53</td>
<td>38</td>
<td>9</td>
<td>6</td>
<td>0.871</td>
</tr>
</tbody>
</table>

Statistically significant differences: ***, p ≤ 0.01; ***, p ≤ 0.001

Table 14. Mean values (standard deviation) for anxiety, depression and health-related quality of life in postmenopausal women with breast cancer at three points of assessment according to randomization group (hormone therapy (HT) or control)

<table>
<thead>
<tr>
<th>HADS anxiety</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HT (n=22-27)</td>
<td>Control (n=19-21)</td>
<td>HT (n=22-27)</td>
<td>Control (n=19-21)</td>
<td>HT (n=22-27)</td>
<td>Control (n=19-21)</td>
</tr>
<tr>
<td>7.52 (5.12)</td>
<td>7.85 (5.23)</td>
<td>5.16 (3.59)</td>
<td>6.40 (3.80)</td>
<td>5.00 (4.49)</td>
<td>5.45 (3.36)</td>
</tr>
<tr>
<td>HADS depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.74 (3.86)</td>
<td>4.90 (3.77)</td>
<td>2.93 (2.93)</td>
<td>3.81 (2.48)</td>
<td>2.85 (3.05)</td>
<td>4.24 (3.19)</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91.82 (10.48)</td>
<td>86.00 (11.66)</td>
<td>90.00 (11.41)</td>
<td>85.67 (12.85)</td>
<td>88.18 (17.81)</td>
<td>86.33 (11.54)</td>
</tr>
<tr>
<td>Role functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>84.85 (26.18)</td>
<td>85.09 (22.15)</td>
<td>91.67 (19.07)</td>
<td>81.58 (26.58)</td>
<td>87.88 (25.81)</td>
<td>80.70 (31.91)</td>
</tr>
<tr>
<td>Emotional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66.67 (27.13)</td>
<td>65.87 (28.61)</td>
<td>79.32 (17.51)</td>
<td>73.02 (24.99)</td>
<td>75.62 (21.05)</td>
<td>71.03 (20.00)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>77.16 (24.96)</td>
<td>71.43 (21.82)</td>
<td>88.27 (16.55)</td>
<td>73.81 (17.14)</td>
<td>83.33 (19.06)</td>
<td>74.60 (23.93)</td>
</tr>
<tr>
<td>Social functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75.00 (28.77)</td>
<td>79.17 (20.86)</td>
<td>82.69 (26.45)</td>
<td>80.00 (22.69)</td>
<td>86.54 (23.58)</td>
<td>82.50 (25.06)</td>
</tr>
<tr>
<td>Inompana</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64.10 (33.89)</td>
<td>51.51 (33.69)</td>
<td>29.49 (30.30)</td>
<td>51.51 (33.69)</td>
<td>39.74 (32.69)</td>
<td>46.97 (35.12)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.63 (21.58)</td>
<td>32.80 (24.21)</td>
<td>26.07 (23.72)</td>
<td>26.46 (20.02)</td>
<td>18.80 (17.15)</td>
<td>26.98 (21.82)</td>
</tr>
<tr>
<td>Global quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61.73 (22.91)</td>
<td>66.27 (19.98)</td>
<td>72.84 (23.41)</td>
<td>65.48 (21.62)</td>
<td>75.31 (21.37)</td>
<td>67.46 (23.11)</td>
</tr>
</tbody>
</table>

*, HADS, The Hospital Anxiety and Depression Scale, range 0–21, high values indicate problems; ***, EORTC QLQ-C30 functioning scales and global quality of life, higher scores indicate better functioning; ***, EORTC QLQ-C30 symptom scales, higher scores indicate more problems.

* Statistically significant difference over time, p < 0.05; **, statistically significant difference over time, p < 0.01;

***, statistically significant difference over time, p < 0.001;

Statistically significant group-by-time interaction, p = 0.0002
Table 15. Mean values (standard deviation) for EORTC BR-23 subscales in postmenopausal women with breast cancer at three points of assessment according to randomization group (hormone therapy (HT) or control)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body image**</td>
<td>77.50 (26.64)</td>
<td>81.44 (16.05)</td>
<td>84.88 (19.20)</td>
</tr>
<tr>
<td>Sexual functioning*</td>
<td>37.18 (27.61)</td>
<td>33.02 (29.57)</td>
<td>37.18 (27.21)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>48.68 (22.93)</td>
<td>57.14 (14.02)</td>
<td>54.34 (30.81)</td>
</tr>
</tbody>
</table>

\* EORTC QLQ-BR-23 functioning scales, higher scores indicate better functioning. \* Item on sexual enjoyment should be responded to only by those who were sexually active, n = 11 in HT group and n = 7 in the control group. \*\* statistically significant difference over time, p < 0.05

There was considerable inter-individual variation and numerical differences between the groups did not reach statistical significance. No statistically significant group by time interaction was found with one exception, Insomnia \[d.f(2.46) F=7.04;p=0.0014\], where problems in the HRT group decreased more and faster than in the control group (Table 14). In the study population statistically significant differences by time were found for HADS anxiety, HADS depression, Emotional functioning, Cognitive functioning, Insomnia, Fatigue, Global QoL, and Body image. HADS anxiety, HADS depression, Insomnia and Fatigue decreased while the functional scales and Global quality of life increased.

Women in the HRT group showed statistical significant improvement for HADS anxiety, HADS depression, and Emotional, Cognitive and Social function (Figure 14). No statistically significant differences over time were recorded for Physical function, Role function and Fatigue in the HRT group. In contrast to the HRT group the only significant change found among the women in the control group was a gradual decline in HADS anxiety. There was also a marked improvement over time in Global QoL in the HRT group. Overall, the major determinants for this improvement were reduction in HADS anxiety (r = 0.79; p<0.001), reduction of HADS depression (r = 0.72; p<0.001) and gain in Emotional function (r = 0.67; p<0.001).
Figure 14. Effects of hormone therapy (HT) on quality-of-life variables in postmenopausal women with breast cancer. Mean values and standard deviations for anxiety (HAD), depression (HADD), emotional function (EF), cognitive function (CF) and social function (SF) as assessed at randomization (1) and after 6 (2) and 12 (3) months. *, $p < 0.05$; **, $p < 0.01$

Figure 15. Effects of hormone therapy (HT) on global quality of life (QL) among women with and without concomitant tamoxifen (TAM; upper panel) and in the total group of postmenopausal women with breast cancer (lower panel) as assessed at randomization (1) and after 6 (2) and 12 (3) months. *, $p < 0.05$; **, $p < 0.01$
Of the total study population, 50 (67%) were on adjuvant treatment with tamoxifen. These women had a lower HADS anxiety level (6.0 ±4.5 vs 9.6 ±4.5; p<0.01) and better Emotional function (72.8 ±24.0 vs 54.3 ±27.7; p<0.01) at baseline as compared to those not being treated with tamoxifen. Among these 50 women, 25 were in the HRT group and 25 in the control group. The same positive effect of HRT on QoL as shown in the total HRT material was also apparent in the subgroup of women with concomitant tamoxifen (Figure 15). Mean values for Global QoL increased from 60.3 ±23.4 at baseline, to 77.5 ±23.2 at 12 months (p<0.01). Women not on HRT, and treated with tamoxifen reported no change in Global QoL over time (mean:61.8 ±17.9 vs 65.6 ±24.9 at 12 months). There was a statistically significant difference (p<0.01) between those on tamoxifen plus HRT and those on tamoxifen only.
5 DISCUSSION

5.1 INFORMATION NEEDS

The two most important findings in paper I were that Swedish breast cancer patients gave highest priority to facts about disease and treatment, i.e. information about cure, stage of disease and treatment options, and that they preferred a collaborative role in treatment decisions. A ranking order, an Information Needs Profile, was created for all eight items of information (Fig 9). The results were essentially consistent when adjusted for age, education, time from diagnosis and for how active patients wanted to be in treatment decisions.

The results were consistent with data from Great Britain and Canada (Davison et al., 1995; Degner et al., 1997; Luker et al., 1995). This does not mean that the other five information categories are of no importance – they are just of less importance. The method of paired comparison is a useful tool to extract a preference order from the patients and to avoid so called “ceiling effects” which means that patients give high priority to all items of information.

The strong request for information was also confirmed in paper III where most women (participants and non-participants) valued all nine items of information about breast cancer and HRT as ‘very important’ when tested with a Likert scale (Table 9). There are several other studies with similar results. In a British study with 2331 cancer patients in different stages of disease more than 90 % answered ‘I absolutely need that information’ or ‘I would like to have that information’ when they valued seven different items of information (Jenkins et al., 2001). Thus it seems that in the clinical situation it is not feasible to evaluate which kind information is most important to patients using Likert scales (Degner et al., 1997).

Only in item 6, ‘information about how oestrogen therapy can affect physical health’ there was a difference between participants and non-participants. More participants (85.5 %) than non-participants (69 %) valued the item as ‘very important’ (p=0.045). The result indicates that health effects from HRT, other than those related to breast cancer, were important for the decision to accept inclusion in a clinical trial.

Using the method of paired comparisons a ranking list (Fig 12 and 13) of the nine items of information was achieved also in paper III. Participants and non-participants in the Stockholm trial had the same three top priorities among the nine items, all three items dealing with hard facts directly related to HRT.

For both groups the first priority was ‘Information about the risk of recurrence of breast cancer with and without oestrogen therapy’ (item 3). This was the primary endpoint of the study and was also the main issue for patients to accept or decline
inclusion. Clearly women had understood the trial information and risk of recurrence of breast cancer was central in their decision.

Also patients’ second and third top priorities ‘Information about new research data about oestrogen therapy and breast cancer’ (item 2) and ‘Information about the reason for not recommending oestrogen therapy to breast cancer patients’ (item 1) represent disease specific information about HRT in relation to breast cancer and not in relation to physical or mental effects in general.

The item ‘Information about how oestrogen therapy can affect sex life’ (item 7) had the lowest ranks among both participants and non-participants, it was less important than the other eight items. However 54.5 % of participants and 43.1 % of non-participants valued the item as ‘very important’ according to the Likert scales (Table 9).

In summary there were no differences in information needs about breast cancer and HRT among participants and non-participants that could predict whether a woman would accept or decline participation in the Stockholm trial.

5.2 PATIENT PARTICIPATION IN TREATMENT DECISIONS

It might seem inconsistent for patients to have a strong preference for disease-related information but to abstain from being active in treatment decisions as shown in paper I and, to a lower degree, in paper III. This was also the conclusion from other studies (Bilodeau and Degner, 1996; Davison et al., 1995; Strull et al., 1984; Sutherland et al., 1989). Physicians seem to overestimate the desire to participate in medical decisions but to underestimate the desire for information (Strull et al., 1984). Active participating in treatment decisions pre-supposes well-informed patients but the strong need to be well informed also reflects other wishes than to take control in treatment decisions. An active approach may be a coping strategy and a way to communicate with the physician regardless of its impact on treatment.

To leave decisions to the physician could reflect a reaction of regression and a wish to be taken care of. Previous experience on physicians’ attitudes in treatment decisions may have affected self-esteem and confidence and reduced the capacity to participate in medical decisions. On the other hand it could also just reflect a high confidence in the competence of the physician. This interpretation is supported by the high degree of agreement (72% in paper I and 66 % in paper III) between how active patients wanted to be and how active they actually were. In the Canadian report only 42 % of the patients reported agreement between their preferred and actual role in treatment decisions (Degner et al., 1997). More patients wanted to be more active than more passive.

The ranking of preferred roles did not agree with the unfolding theory of an underlying dominant psychological dimension of keeping-sharing-giving away control (paper I). The majority of our patients had preference orders of roles describing collaboration (B, C and D), which suggests the existence of a new pattern, namely that of collaboration.
In paper I we defined a collaborative patient as preferring roles B+C+D (Fig 7). Previously active patients were defined as those preferring A+B, passive patients by D+E and collaborative by C (Degner et al., 1997). Also with that definition the Swedish patients had more “passive preferences” than British and Canadian patients (Beaver et al., 1996; Bilodeau and Degner, 1996; Davison et al., 1995; Degner et al., 1997). More patients in Sweden preferred D+E (66%) than patients in the UK (52%) and Canada (58%, 43% and 34%, respectively).

The card sort procedure and the method of paired comparisons regarding patient roles yield a preference order of the five roles. In the clinical situation, however, the method is too complex and time consuming. Patients’ first preferred role is more relevant to the clinician and in paper III we used a pick-one method for first preferred role, just as for ‘actual role’ in paper I, a method that has been successfully used by others (Neufeld et al., 1993; Strull et al., 1984; Sutherland et al., 1989).

The majority, of all patients 68% preferred the role C (73 % of participants and 63 % of non-participants) in paper III. In comparison in paper I only 21 % chose C and in reports from Degner 44 % chose C (Degner et al., 1997).

In patients preferring B+C+D as many as 98 % would be defined as collaborative. The higher percentage for role C in paper III could have been influenced by the offer to participate in a clinical trial.

Only 60 % of participants in the Stockholm study were content with their actual role compared to 72 % of non-participants. Among participants 37% wanted to be more active and only 2 % more passive. This confirms the picture of the more active patient in the group of participants in the Stockholm study.

The fact that the majority of women preferred some degree of a collaborative role indicates a desire to communicate and puts a demand on doctors to learn effective and sensitive communication skills.

The hesitation to take responsibility in treatment decisions, especially those reported in paper I, is interesting in the light of the present ethical debate in the Western world, with a shift from paternalism towards increased respect for the autonomy and competence of the patient. Political promises are made about increased patient participation in treatment decisions and improved patient information as a means of strengthening patients’ rights.

It is urgent that we learn more about patients’ own preferences. Research in medical decision-making is an important tool to evaluate effects of change in routines and legislation and to study possible development in patients’ preferences over time. New generations and groups of patients with changing values or different educational or cultural backgrounds are continuously introduced into the healthcare system. On the basis of our results, we suggest that the preference of the “modern patient” is not to take control over treatment decisions but to communicate with the physician and to demand collaboration.
Further research is needed to analyse the importance of patients’ preferences in decision-making by using simpler methods and to find ways of optimizing the information-giving process. The role of new media, internet and interactive techniques should be investigated. It is important to follow the development towards more open communication and increased patient participation and to be attentive to signs of psychological harm or discontent.

5.3 THE MEANING OF BREAST CANCER

*Challenge* was the most frequently chosen meaning of illness among all patients in the study and especially among patients in middle life ([paper II](#)). Today, most newly diagnosed breast cancer patients will be cured by surgery and adjuvant therapies (Bergh et al., 2001). When women get the information about their disease they rank “chance of cure”, “stage of disease” and “treatment options” highest ([paper I](#)) (Degner et al., 1997). This will help to adopt a realistic attitude – managing uncertainty becomes a major challenge.

Some patients who chose *challenge*, stressed that closer to the time of breast cancer diagnosis they would have chosen another category. They said: “*challenge* now – but all categories have been present during the process, *punishment or enemy* between surgery and other treatment”. Statistically however, there were no significant differences regarding time from diagnosis which was consistent with the Canadian study (Degner et al., 2003).

Patients who wanted to be active or cooperative in relation to their physician did not chose *challenge* more often than other patients. However, it is interesting to note that, in contrast to data from Lipowski, some Swedish patients had an active interpretation of other categories than *challenge*. Thus, in some women the interpretations of *challenge* and *enemy* came very close – one patient explained; “*challenge*, in fact an *enemy*, but it will be defeated”. This is in contrast to the central point in Lipowski’s interpretation of *challenge*: “disease is viewed as an invasion by inimical forces, internal or external… the usual emotional concomitants of this meaning are anxiety, fear and/or anger” (Lipowski 1970). Most of our patients who chose *enemy* confirmed this interpretation of *enemy*.

The few patients with incurable breast cancer (stage 4) clearly chose their meaning of illness from the group enemy/punishment/irreparable loss/weakness. However, in our clinical experience, many patients in this situation keep on working through their losses, bravely fighting against hopelessness.

Nine patients out of 29 that chose *irreparable loss* explicitly meant the loss of a breast.

Most likely this reflects the fact that a breast cancer diagnosis has a particular psycho-sexual dimension in women. The breast is associated with attractiveness, sexuality, fertility and motherhood. Lipowski interprets the choice of *irreparable loss* negatively with a risk of “depression, hostility and resistance to rehabilitation measures, even to suicide” (Lipowski, 1970). This seems to be an over interpretation of the choice *irreparable loss*. In the rehabilitation process following a breast cancer diagnosis,
patients’ grief, mourning and search for new goals must be respected. Other patients, however, broadened the concept and described the irreparable loss of “health”, “safety” or “life.

As many as 14 patients chose value, most of them were more than 65 years old (data not shown). Their choice perhaps reflects a process of realizing that life needs caring for as long as it lasts. The experience of breast cancer might have highlighted that process.

Obviously some patients who chose relief interpreted the word differently from Lipowski (Lipowski, 1970). Patients felt relief: “to know what was wrong”, “not to need radiotherapy”, “to get rid of it” and “that it is over”. This is not what Lipowski meant: “a welcome respite from demands and responsibilities of being well or from some current interpersonal crisis or economic problem”.

Strategy was interpreted as “you have to reconsider – it means changes – think about how to handle the situation” and “it’s close to challenge”. This reflects attitudes of resistance and adjustment and seems far from Lipowski’s interpretation: “Being sick and disabled is used as a technique to secure attention, support and compliance from others” (Lipowski, 1970).

In Canada and Great Britain challenge was chosen by even more patients (57% and 62%) than in Sweden (33%). (Degner et al., 2003; Luker et al., 1996). This may reflect cultural differences and more active breast cancer patients regarding preferred roles (Beaver et al., 1996; Degner et al., 1997).

The same eight meanings of illness were tested in a Canadian study of patients with advanced cancer (Barkwell 1991). The most common categories of meaning were challenge (36%), punishment (23%) and enemy (20%). Patients who selected challenge had lower pain, higher coping and lower depression scores than those who selected enemy or punishment.

It is interesting to note that in the present material there was a greater determination to stay active and fight against the disease than in Lipowski’s interpretation (Lipowski, 1970). Comparing women of our time to those of the 1970’s general education is better today and women are more likely to work in a profession. Certainly this could influence the woman’s image of herself as a patient. The patient-doctor relationship is becoming more cooperative with better-informed patients.

Lipowski’s eight categories describing meaning of illness are not useful without also asking the patient to interpret the category chosen. However, to offer patients the opportunity to express and describe their view freely, and in their own words, will always be meaningful as one of the many pieces in the complex basis of successful communication.
5.4 PARTICIPANTS AND NON-PARTICIPANTS IN THE STOCKHOLM STUDY

Most cancer clinical trials have a focus on therapeutic efficacy with time to progression or overall survival as primary end points which means to live as long as possible in spite of a diagnosis of for instance breast cancer. Patients accepting inclusion in the Stockholm trial were however prepared to be randomized to a treatment that might increase the risk of breast cancer recurrence with a possible reduction of life expectancy. The gain would be an increase in quality of life and positive health effects on other aspects than breast cancer. In paper III we found that women accepting or declining this scenario made rational decisions. Participants in the Stockholm trial had a lower risk of recurrence than non-participants. They had smaller tumours than non-participants, fewer patients had stage 2-disease with lymph node metastasis and fewer had been treated with adjuvant chemotherapy (Table 8). Participants were older than non-participants and more time had elapsed since their breast cancer diagnosis. Women who were at a higher risk of recurrence declined participation in a study. Risk of recurrence was an important reason also for women who declined participation in the British feasibility study with HRT to breast cancer survivors16 and in a similar study in the US (Vassilopoulou-Sellin and Klein, 1996).

More participants used HRT at breast cancer diagnosis compared to non-participants. They might have a previous experience of beneficial effects. The reason for accepting inclusion was however not an issue in this study. The Stockholm study did not have menopausal symptoms as an inclusion criteria but symptoms were recorded for 46 participants and 28 non-participants and there was no significant difference between the groups (82.6% vs 75.0%) (Table 8). Other studies have demonstrated an increased interest to participate in trials with HRT among women with estrogen deficiency symptoms, low QoL or osteoporosis in the family (Marsden et al., 2000). In a HRT-study in the US, 56% of breast cancer survivors accepted to take HRT only if they had severe menopausal symptoms and the increased risk of recurrence was small. To achieve a decreased risk of hip fracture and heart attack was much less important (Ganz et al., 1999).

5.5 ATTITUDES TO PARTICIPATION IN CLINICAL TRIALS

There were apparent differences in attitudes to participation in clinical trials (paper III) (Tables 10 and 11). Participants were more prepared to accept uncertainty (statement no. 5) and to have an altruistic attitude to participation in research (statement no. 6) (Table 10). There are several reports about altruism as a reason for patients to join a cancer clinical trial (Cassileth et al., 1982; Ellis, 2000; Slevin et al., 1995). Still according to a review on this subject it is more common to participate in ones’ own interest (Ellis, 2000). This was confirmed in the present study where participants proved to be more prone to accept an increased risk of recurrence in breast cancer if their quality of life or health in general was improved (statement no. 10 and 12, Table 10).
Non-participants did not accept an increased risk of recurrence in breast cancer confirming that a fear of unacceptable side effects is a main reason for patients to decline participation in cancer clinical trials (Jensen et al., 1993). Anxiety not to get the best treatment, dislike of the hazard at randomisation and a wish that the physician decides which treatment is best have also been reported as reasons for patients to decline participation in Trials (Jenkins and Fallowfield, 2000).

Results were similar for the questionnaire developed by Slevin (Table 11) as participants again demonstrated an altruistic attitude (statement no. 2) and were more prone to accept risks as they saw participation in research as a better chance to get new and experimental treatments (statement no. 4 and 8). This corresponds to the results in the original study by Slevin where patients with different cancer diagnoses were interviewed. Participants were also more prepared to accept that treatment was decided by a panel of experts instead of by her doctor (statement no. 1) which is also in agreement with patients in the original Slevin study (Slevin et al., 1995).

Thus there was agreement between the results from the two questionnaires regarding patients’ attitudes to participation in clinical trials. Patients who accepted to be randomized to HRT or no treatment seemed to be more prepared to take risks, even the risk of relapse in breast cancer, to accept uncertainty, to have an altruistic attitude about benefits for future patients and to value health effects in general and quality of life higher than women who declined participation.

5.6 HEALTH RELATED QUALITY OF LIFE IN THE STOCKHOLM STUDY

Progress in treatment and mammographic screening programs have improved the prognosis of breast cancer. Currently the latest five-year survival rate published from the Stockholm County Council is 90 % for women diagnosed between 2000 and 2004 (Figure 5 page 4).

Consequently there has been a dramatic increase in the number of breast cancer survivors. Many women with breast cancer will receive treatments that cause severe menopausal symptoms from e.g. chemo- and endocrine therapy (Bachmann, 1999; Fellowes et al., 2001; Goodwin et al., 1999; Nystedt et al., 2000). Also postmenopausal women with a breast cancer diagnosis are denied to use HRT. There is an increasing interest in quality of life issues among this growing group of patients. Thus, the management of menopausal symptoms in breast cancer survivors is an important clinical concern (Hickey et al., 2005b). HRT is well known for its beneficial effects on QoL in healthy women (MacLennan et al., 2001). On the other hand the effects of HRT on QoL in women with breast cancer have not previously been reported.

After twelve months of treatment there were few group differences between women using HRT and those who did not (paper IV). Only insomnia was positively affected by HRT. However, among women within the HRT group there was apparent improvement and higher scores on most functional variables and Global quality of life, and lower scores on the symptom scales. No such effect was recorded within the control group not using HRT. Apparent explanations for the lack of more group
differences are inter-individual variation and the small sample that could be analysed over time. The study was stopped, and the number of patients intended to be included was not reached. Data suggest however that the controversial treatment with HRT may improve QoL also in women with breast cancer. A larger study is needed to further investigate effects of HRT in breast cancer patients. The fear of a possible recurrence in breast cancer due to HRT did not seem to impair quality of life for patients in the treatment arm.

Tamoxifen is frequently used as an adjuvant treatment in hormone-receptor positive breast cancer. It is known for its estrogen-like effects on bone, uterus and possibly even the brain (Ganz, 2001). The properties of tamoxifen and information about them as well as knowledge about the overall better prognosis for hormone receptor positive tumors, could tentatively explain the findings that women on tamoxifen had lower HADS anxiety levels and better Emotional function at baseline. However, during the 12 months study no further change was noted in any of the variables among women in the control group who were on tamoxifen only. In contrast when HRT was added there were several additional positive effects. In fact the effect was quite similar to that in women not on tamoxifen. HADS anxiety and HADS depression levels were reduced and Emotional function was improved. These factors were also strongly associated to the positive change in overall QoL and the significant difference between groups.

Women with breast cancer are currently advised against using HRT (Antoine et al., 2007; Holmberg et al., 2008; Kenemans et al., 2009; von Schoultz and Rutqvist, 2005). There is however little evidence either for strong recommendations for or against HRT in this setting due to lack of reliable studies. The importance of sex hormones in the patho-physiology of breast cancer is well established and anti-estrogen therapies are major principles for treatment. Treating menopausal symptoms in breast cancer women with HRT must be done with great caution (Antoine et al., 2007; Baber et al., 2005; Gainford et al., 2005) Physicians in collaboration with patients have often tried different alternative measures such as phytoestrogen, black cohosh, SSRI and clonidine for symptomatic relief. Unfortunately these remedies have had only limited effect, sometimes even adverse side effects (Ganz, 2001; Harris et al., 2002; Hickey et al., 2005a). In a recent review (Franke et al., 2007) a preferential order of treatment modalities for severe menopausal symptoms in breast cancer survivors was suggested. Life style advice was the first line of treatment and non-hormonal alternatives second line. Only as a third option for carefully selected women with severe menopausal symptoms HRT was suggested for a maximal duration of five years.

Quality of life issues in breast cancer survivors is a clinical problem of growing magnitude. There is a great need to find new treatment strategies for effective relief of the many symptoms and adverse consequences of estrogen deficiency (Lewis, 2009). The development of anti-progesterone and estrogen combined with anti-estrogen therapy holds promise for the future (Engman et al., 2008; Kontos et al.). In healthy women the risk of estrogen alone is much less than for combined estrogen/progestogen therapy (Conner et al., 2008). It could be that estrogen alone is reasonably safe in selected groups of women with breast cancer e.g. those on concomitant tamoxifen treatment. Tibolone in combination with tamoxifen did not increase recurrence while a
clear negative effect was seen in women on aromatase inhibitors (Kenemans et al., 2009). In estrogen deprived women treated with aromatase inhibitors progestogens only could possibly be an alternative (Cline et al., 1998). Clearly all these speculations will need to be carefully evaluated in randomized trials.

While further development in the field and larger studies are needed so far our data suggest that the controversial treatment of HRT may have a potential to improve several factors of importance influencing QoL in women with breast cancer. Whether such improvement in some selected women may outweigh a possible increase in breast cancer recurrence should be most carefully discussed between the woman and her physician. After thorough information and consideration the final decision should be made by the woman herself.
6 GENERAL CONCLUSIONS

Information needs are strong among breast cancer survivors with the highest priority for disease specific items of information – chance of cure, stage of disease and treatment options. This does not mean that other information is not important – just less important. The method of paired comparison is a useful tool to assess patients’ information needs.

Breast cancer survivors irrespective of age, education and time from diagnosis prefer a collaborative role with their physician in treatment decisions. Physicians seem to overestimate the desire to participate in medical decisions but to underestimate the desire for information. It is urgent that we learn more about patients’ own preferences. New generations and groups of patients enter the healthcare system. Data suggest that the preference of the “modern patient” is not to take control over treatment decisions but to be well-informed about disease and treatment, to communicate with the physician and to demand collaboration.

Most breast cancer patients chose challenge as their perceived meaning of illness with enemy and irreparable loss as second and third choices. Next choices were in the following order: punishment, weakness, value, relief and strategy. The choice of challenge may depend on time since breast cancer diagnosis. Irreparable loss reflects the fact that a breast cancer diagnosis has a particular psycho-sexual dimension in women. Most of the women choosing value were more than 65 years old. To stay active and fight against the disease may reflect the woman’s image of herself as a patient.

Breast cancer survivors accepting participation in a clinical trial with HRT were more prepared to accept uncertainties and risks, including the risk of a recurrence in breast cancer, if their quality of life or general health was improved. They also had a more altruistic attitude compared to those who declined participation. Women made rational decisions whether to participate or not – participants had a lower risk of recurrence in breast cancer than non-participants. When offered participation in a clinical trial with HRT the top priorities of information were about hard facts related to HRT – risk of recurrence, new research about HRT and evidence about advising women treated for breast cancer against HRT. This confirms the image of the well-informed patient.

Breast cancer survivors randomized to HRT experienced an improvement in Insomnia compared to the control group without treatment. Within the HRT-group there was an improvement over time for several quality of life variables and global QoL. HRT added to tamoxifen significantly increased global quality of life compared to tamoxifen alone in the control group. Quality of life issues in breast cancer survivors is a clinical problem of growing magnitude. There is a great need to find new treatment strategies for effective relief of the many symptoms and adverse consequences of estrogen deficiency.
Data suggest that the controversial treatment of HRT may improve QoL in women with breast cancer. Whether such improvement in some selected women may outweigh a possible increase in breast cancer recurrence should be most carefully discussed between the woman and her physician. After thorough information and consideration the final decision should be made by the woman herself.
7 CRITICAL ASSESSMENTS AND FUTURE PROSPECTS

The results presented in this thesis should be interpreted with some caution. Data were collected from a limited number of patients and over a time period partly different from now. Attitudes towards health and disease, medical care, communication and patients rights are dynamic and highly influenced by the political, public and ethical debate in the society. Breast cancer is probably one of all diseases that attracts most attention in mass media and on the internet. Patient organisations have, rightly so, gained a lot of influence and are key players as lobbyists for more resources. The amount of information about breast cancer is limitless. Women’s high priority of hard facts about breast cancer was apparent already during the start of the period examined and is not expected to be less clear today.

Out of the 261 women recruited in paper I and II only 201 were interviewed. Thus the drop out rate was almost 25%. Information about reasons to reject participation was obtained for only 29 of them. To many women the first months after a breast cancer diagnosis are characterized by strong emotions, chock, agony, anger and despair. As many as 83 women were interviewed within the first six months after diagnosis and this fact could well have biased their perceptions about information needs. Still the three top ranked items i.e. chance of cure, stage of disease and type of treatment were seemingly unaffected by time since diagnosis and also by the woman’s preferred role. The coefficient of consistency was very high. The results are also supported by similar findings previously reported by other groups.

During the study period there has been an intense discussion on patient’s rights including the right to influence treatment and the choice of care giver. Evaluation and grading of care givers are open to the public in order to influence patient’s activity and facilitate her choices. This puts a pressure on the patient to be better informed and on care givers to improve their competence and communication skills. Probably patients of 2010 would have more active preferences than accounted for in our study.

Certainly intrapersonal, disease-related and environmental factors may influence a patient’s subjected meaning of illness. However the eight different categories for “meaning of illness” according to Lipowski were defined more than forty years ago. Furthermore they were tested in Canada in women with advanced breast cancer. Here also most women investigated were free from recurrence. Given the rapid and dynamic change in attitudes and values these categories may not be relevant to the modern patient of our time. In fact some patients did not agree with the original interpretations of e.g. relief and strategy. Still it seems reasonable that most patients chose challenge as their perceived meaning of illness and that this choice may be affected by age and stage of disease. Furthermore there was little difference in the results when categories were regrouped and tested according to Degner et al. A few patients in paper I and II
were in stage 4 when they by mistake were included in the study. This was apparent when data for paper II were analyzed. It was decided not to exclude them as their of “meaning of illness” was worth commenting although they were few. However it is not correct to identify them as breast cancer survivors.

Interviews about participation in the Stockholm trial with HRT were accomplished during a time when the debate about benefits and risks of HRT shifted almost from one extreme to the other. This has been reflected in mass media, in scientific literature and in the attitudes of physicians prescribing HRT. The number of patients in paper III is however too small to be analyzed with respect to time. Also those willing to participate in the trial more often were previous HRT users. Thus they would be expected to have had more climacteric symptoms and possibly a worse quality of life. Certainly this difference between groups could have influenced their attitudes and the overall results. Still all patients’ high priority of hard facts about breast cancer and HRT was apparent and is expected to be as clear today.

For the future the informed consent process associated with clinical trials would need further evaluation and improvement. The large amount of information that patients must be given according to present guidelines needs evaluation - is to any benefit of patients or too much of a burden. Written patient information needs evaluation. Is it written to facilitate the understanding of the patients or mainly to satisfy legal concerns of the sponsor of the trial? Is the language understandable and the content relevant for the average patient. Interactive techniques and other means to deliver patient information need testing and evaluation.

The clinical material in the study on HRT and quality of life in breast cancer survivors was apparently too small to allow firm conclusions. Recruitment was hampered as authorities decided to stop the trial preterm. Now only insomnia showed significant improvement between groups whereas other numerical differences did not reach statistical significance. Most likely a larger material would have shown improvement by HRT also for some other variables. Thus within the HRT group there was improvement for several items and for global quality of life. Also there was a significant between groups effect of HRT on global quality of life in combination with tamoxifen.

From a medical point, there is a great un met need of new and safe methods to treat menopausal symptoms and other side effects of treatment. Patients’ assessment of risk and uncertainty and of their weighing of quality of life contra length of life needs further investigation.

New generations of patients and patients from other cultures are gradually introduced as consumers of health care. The competence of physicians and nurses to communicate needs continuous education and training.
8 ACKNOWLEDGEMENTS

I want to express my gratitude to the following persons who in different ways contributed to the completion of this work. My most sincere appreciation goes to:

The breast cancer patients participating in these studies, for taking your time and effort and for sharing your experiences with us.

All breast cancer patients for making my clinical daily work so very meaningful. You teach me continuously about your reality and I deeply admire your strength and ability to live with breast cancer.

Christina Bolund my co-supervisor and former supervisor who introduced me into research in decision-making and helped me realize the first two studies of this thesis and create the necessary conditions for the third study. I appreciate your creativity and your effort always to emphasize the psychosocial aspects of living with cancer. Your life-work, the Psychosocial unit and EPOR at Radiumhemmet, of such enormous importance to our patients. May it be maintained and well cared for in the future!

Nils Wilking my present supervisor who helped me so much to finalize this work. As former head of the Breast cancer unit of Radiumhemmet you were the first to suggest that I "made science" out of my former experience in journalism and my passion for issues of information and you engaged in being my co-supervisor. You are a true entrepreneur in the best sense, seeing possibilities and getting things started. Later when I needed extra support you became my supervisor and I deeply appreciate your assistance and your belief in me since then. I am so happy for the halts in Stockholm on your round-the-world lecture tours.

Eva von Schoultz my former colleague at the Breast cancer unit of Radiumhemmet for, together with Nils, standing by my side when I needed focus on something concrete to work for. You never failed in giving me support to believe it was possible to accomplish. Your well structured and successful way of working is worth all respect and serves as an ideal to me. Thank you also for giving me access to your husband Bo - in the sense of his profound experiences in interpreting and writing science. You are a dream team together and Eva, you belong to my special group of sisters.

Jonas Bergh former head of the Breast cancer unit of Radiumhemmet for engaging as my financial supporter during the final stage of this work. I am not used to be dependant on a financier and I deeply appreciate that you believed in me enough to risk “ALF-medel” in completing this project. Maybe it is time for some profit. You are also my "champion" regarding knowledge of breast cancer - the clinical trial that you cannot account for in detail is not worth mentioning and your curiosity of the inner secrets of cancer cells seems endless. I miss our many, sometimes provoking, discussions during the years and sincerely hope that you will move back to Stockholm from Great Britain.
Bo von Schoultz for giving me the opportunity to share your knowledge of hormones and your skill to summarize scientific data and write science. You would no doubt also have been a successful journalist. I am fascinated by your sparkling enthusiasm over “papers” and I am deeply grateful for the time and effort you spent with this work.

Ulrik Ringborg former head of Radiumhemmet for giving me the opportunity to research and for encouraging me to complete this thesis.

Mariann Iiristo present head of the Breast cancer unit for creating possibilities for me to accomplish this book. I truly appreciate your enthusiasm and willingness to accept the challenge of your leadership, for not seeing us as a “mission impossible”.

Helena Michelson, Marianne Nystedt, Yvonne Wengström, Ulla-Britt Torslund, Anna-Maria Hall and Gunvor Svensson for your skilful work with patient interviews.

Mia Fahlen co-author who contributed equally and so well with me to paper IV.

Other co-authors: Helena Michelson, Marianne Nystedt, Kjell Carlström and Yvonne Brandberg for invaluable contributions to the papers.

Lotta Larsson and Mats Hellström for excellent work in sorting out a stack of references and digital pieces of manuscript and transforming all of it into a real book.

Bo Nilsson and Per Näsman for excellent work in the art of statistics.

My present and former colleagues at the Breast cancer unit for friendship, for all your serious work with our patients, for fruitful discussions at our conferences and last but not least for laughs and gossip in the coffee-room. Pleased to see that you have not succumbed to extra work due to my “research vacations”: Annelie, Annika, Brita, Ed, Elisabet, Erika, Jan, Judith, Louise, Marita, Micke, Sigurd, Theo, Tina, Thomas, Tomas and Ylva.

Judith for the skilful manner that you have taken care of a breast cancer survivor that is very important to me – just as you are. You are such a good, just and warm-hearted person – just cut out for being a doctor and a close friend.

Annika my friend and room-mate in Z4 for lots of laughter and good team work when we shared the administrative responsibility for the Breast cancer unit. Just as much as I like your wit and ability to formulate our frustration when things go against us, I appreciate your serious work with our patients.

Jenny, Monika and Sara – for the pleasure you have given me as your clinical tutor. If everyone in the younger generation of oncologists is like you, our future patients can feel a deep trust.

All colleagues of different professions at the Psychosocial unit of Radiumhemmet who taught me so much and “made my ears grow” in communication with patients.
Eva for the good team work and all the fun when you were “chief nurse” for our unit and I had a less precisely identified administrative task, you became a dear friend. I will never forget all your sms when I needed them most.

All nurses at our unit for your dedicated work, Katarina who replaced Eva so successfully, Anneli, Eva, Ingegärd, Kerstin, Lilian, Lotta, Malin, Maria, Sara, Tove and from KPE Gunvor, Catharina and Ingrid. Our secretaries Linda, Monica and Pia. You mean so much to our patients and to me.

Birgitta, retired now, for all our work together with patients at the mammography screening. We were a real team then and I will never forget your support and all the sms.

From the bottom of my heart I want to thank my “extended family” for all your friendship and support. Thanks to you I have a family of sisters, brothers and “bonus children” – Agneta, Christer, Elda, two Gunillas, two Lena, Leyla and Nicke, Malena and Leif, Margita and Claes, Maria and Per, Markku, Mimmi, Peggy and Bo, Tiuu, Gunnell and the “dinner junta” including another Gunilla, Gun-Louise, two Kerstins and Solveig.

Monica my cousin and “half-sister” who many years ago took a big step into my life and heart. I so much appreciate your presence there.

My thoughts go to my parents Margit and Harry and my sister Gunilla. I feel your greetings from heaven.

This study was supported by grants from the Swedish Cancer Society, the Stockholm Cancer Society, the King Gustav V Jubilee Fund, Karolinska Institutet Research Fund, the Swedish Research Council and the Stockholm City Council.

Jonas Bergh’s research group is supported by grants from the Swedish Cancer Society, the Stockholm Cancer Society, the King Gustav V Jubilee Fund, the Swedish Research Council, the Stockholm City Council, Karolinska Institutet and the Stockholm County Council Research Strategy Committee, the Swedish Breast Cancer Association (BRO), the Karolinska Institutet Research Funds and Märit and Hans Rausing.
9 REFERENCES


1931, Reichsgesundheitsblatt, p. 174-175.


Arving, C., B. Glimelius, and Y. Brandberg, 2008, Four weeks of daily assessments of anxiety, depression and activity compared to a point assessment with the Hospital Anxiety and Depression Scale: Qual Life Res, v. 17, p. 95-104.


Bergentz, S. E., 1997, [50 years since the Nuremberg code. Physicians under the Nazi regime were no reluctant servants]: Lakartidningen, v. 94, p. 2692-5.


Bloom, H. J., and W. W. Richardson, 1957, Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years: Br J Cancer, v. 11, p. 359-77.


Christakis, N., 2001, Death Foretold; Prophecy and Prognosis in Medical Care: Chicago and London, University of Chicago Press.


Fallowfield, L., and V. Jenkins, 1999, Effective communication skills are the key to good cancer care: *Eur J Cancer*, v. 35, p. 1592-7.


Ford, S., L. Fallowfield, and S. Lewis, 1994, Can oncologists detect distress in their outpatients and how satisfied are they with their performance during bad news consultations?: Br J Cancer, v. 70, p. 767-70.


Jenkins, V., and L. Fallowfield, 2000, Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy: Br J Cancer, v. 82, p. 1783-8.


Kontos, M., O. F. Agbaje, J. Rymer, and I. S. Fentiman, What can be done about hot flushes after treatment for breast cancer?: Climacteric, v. 13, p. 4-21.


