Doctoral Thesis for the Degree of Doctor of Medical Science

Quality of life and psychological reactions in women on first line chemotherapy for metastatic breast cancer. Correlations to tumour response and predictive factors

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With love to Patric
                Robin
                Marcus

ABSTRACT

Background: Health-related quality of life (HRQoL) is an important endpoint in clinical trials and as an aspect that must be considered in the treatment of patients with metastatic breast cancer. Treatment efficacy and toxicity are important factors for HRQoL, so it is imperative to study the effects of oncological treatment in terms of HRQoL. Different individuals experience different side effects, and genetic variation may affect the metabolism of certain chemotherapy drugs. Single nucleotide polymorphism (SNP) is the most common type of genetic variation in the human genome, and studies have shown that functional genotypes may be an underlying cause of severe chemotherapy toxicity. Prognostic factors are used to choose adequate treatment for the patient. Previous studies of metastatic breast cancer have shown that HRQoL data can predict response, time to progression, and survival. We have only limited knowledge of how patients experience their situation at the point of disease progression after first-line chemotherapy, and so there is a need to further investigate this area in order to better understand and support women with advanced-stage disease.

Aim: All four studies in this thesis were based on the TEX study. The aim was to study HRQoL and psychological reactions in women with metastatic breast cancer receiving chemotherapy. HRQoL was investigated as a prognostic factor for tumour response, progression-free survival, and overall survival; and the relationship between HRQoL, toxicity, and selected biological variations (SNPs) was also examined.

Patients and methods: In the TEX trial, 287 patients with locally advanced or distant metastatic breast cancer were randomized to either epirubicin and paclitaxel (ET) or epirubicin, paclitaxel, and capecitabine (TEX). Treatment was repeated every three weeks. HRQoL was assessed by the EORTC-QLQ C30 and EORTC QLQ-BR23 questionnaires at five points during nine months. Both quantitative (studies I-III) and qualitative (study IV) methods were used. Study I included 163 patients who answered the questionnaire at all five assessment points. Linear regression analysis was used to examine differences in HRQoL between the two groups, over time, and interactions between group and time. Study II included 252 patients who answered the questionnaire before randomization. Logistic regression analysis was used to examine whether HRQoL could be an independent prognostic factor for response to treatment, progression-free survival, and overall survival.

Study III included 185 patients who answered the questionnaire at the two-month assessment and provided blood samples for the genotyping analyses. Multiple regression analysis was conducted to investigate if there were any correlations between HRQoL and toxicity, specific SNPs and toxicity, and SNPs, toxicity, and the impact on quality of life. Finally, Study IV was based on interviews with 20 patients; content analysis was used to analyse the data.

Results:

Study 1: At nine months, the groups showed a statistically significant difference in overall quality of life and physical function, in favour of patients treated with TEX. There were no other differences or interactions between the treatment groups.

Study II: Fatigue was correlated with response to treatment and overall survival. There were also associations between several variables and response (role functioning, social functioning, nausea and vomiting, and anorexia). The analysis showed no association between HRQoL and progression-free survival.

Study III: Statistically significant associations were found between several of the HRQoL variables and toxicity (fatigue, pain, dyspnoea, cardiovascular problems, gastrointestinal problems, and skin problems). Toxicity was also associated with specific SNPs that may affect the metabolism of the drugs used in the TEX trial. There is a connection between SNPs, toxicity, and HRQoL.

Study IV: Many of the women had suspected that their cancer was progressing. Worry was the most common reaction. The women had many different strategies to deal with the situation, and the majority of them understood and accepted their situation. Interest in professional counselling was small, and many reported that they felt that their first relapse was more traumatic.

Conclusion: HRQoL over time provides information that can be used in the choice of treatment, especially if no difference can be demonstrated in treatment response between the chosen treatments. Frequent quality of life measurements at different times give increased knowledge of patients' needs, allowing practitioners to better provide support and care during the course of disease. The analysis showed a relationship between fatigue and response to treatment and overall survival. The results also show that as patients' progress through treatment, they develop resources to deal with difficult information and do not necessarily express a need for professional psychosocial support. The analyses revealed an association between HRQoL and toxicity, between specific SNPs and toxicity, and between SNPs, toxicity, and the impact on quality of life. Such knowledge may influence the choice of chemotherapy in this patient population, depending on the treatment's toxicity profile and its impact on patients' quality of life.

LIST OF PAPERS

This thesis is based on the following four papers, which are referred to in the text by their Roman numerals.

I. Svensson H, Einbeigi Z, Johansson H, Hatschek T, Brandberg Y.
Quality of life in women with metastatic breast cancer during nine months after randomization in the TEX trial (epirubicin and paclitaxel w/o capecitabine)
Breast Cancer Research Treatment 2010; 123(3):785-79.

II. Svensson H, Einbeigi Z, Johansson H, Hatschek T, Brandberg Y.
Health related quality of life as prognostic factor for response, progression-free survival and survival in women with metastatic breast cancer.
Medical Oncology, in press 2011

III. Svensson H, Brandberg Y, Hatschek T, Skrtic S , Enerbäck C, Einbeigi Z.
Specific single nucleotide polymorphisms as predictor of toxicity at chemotherapy in women with metastatic breast cancer and its association with health-related quality of life.
Submitted for publication

IV. Svensson H, Brandberg Y, Einbeigi Z, Hatschek T, Ahlberg K.
Psychological reactions to progression of metastatic breast cancer –
an interview study. *Cancer Nursing 2009; 32(1):55-63.*

ABBREVATIONS

CI	Confidence interval
CTC	Common Toxicity Criteria
CTO	Clinical Trial Office
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire-C30
EORTC QLQ-BR23	The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer Specific module-BR-23
ER	Estrogen receptor
ET	Epirubicin and paclitaxel
FEC	Fluorouracil, Epirubicin and cyclophosphamide
HER2 or HER2/neu	Human Epidermal growth factor Receptor 2
HRQoL	Health-related Quality of Life
PFS	Progression-free survival
PgR	Progesterone receptor
RECIST	Response Evaluation Criteria in Solid Tumors
SBG	Scandinavian Breast Group
SNP	Single nucleotide polymorphisms
SweBCG	Swedish Breast Cancer Group
TEX	Epirubicin, Paclitaxel and Capecitabine
TTP	Time to progression
WHO	World Health Organization
WHOQOL	The World Health Organization Quality of Life group

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INTRODUCTION

Breast cancer

Epidemiology

Breast cancer is the most common cancer among women in Sweden. The incidence is increasing by 1.2 % per year during the last two decades but at the same time period, breast cancer mortality has decreased. A total of 7380 women developed breast cancer in Sweden during 2009 (Socialstyrelsen 2010). Approximately 10% of all Swedish women will develop breast cancer during their lifetime, and 25% of these are expected to develop metastatic disease. Several factors have contributed to the improvement of survival, particularly earlier diagnosis since the introduction of general mammography screening, increased public awareness, and last but not least, more effective treatment for both early and metastatic breast cancer (Esserman et al 2009). The relative survival rate for breast cancer five years after diagnosis is currently 86% in Sweden (Engholm et al 2010).

Etiology

Many factors influence the risk of developing breast cancer. Most of them are related to fertility and reproductive factors. The risk is increased by early age at menarche, late age at menopause, late age at first childbirth, null parity, and a short breastfeeding time (Key T et al 2001, Veronesi et al 2005), as well as use of oral contraceptives (Collaborative Group on Hormonal Factors 1996, Key T et al 2001) and hormone replacement therapy (Key T et al 2001, Porch JV et al 2002), particularly the combination of oestrogen and progesterone. Other risk factors are age, heredity, and ionizing radiation (Veronesi et al 2005, Heyes et al 2009). Lifestyle factors such as being overweight after menopause, high alcohol consumption, and physical inactivity also appear to increase the risk of breast cancer (Carmichael et al 2006, Li et al 2009, Peplonska et al 2008).

Heredity

Hereditary breast cancer is characterized by early-age onset, occurrence in multiple family members, and occurrence of bilateral breast cancer or breast and ovarian cancer in the same woman. Studies of the Swedish Family Cancer Database have indicated that genetic factors may

account for 25% of breast cancer variation (Czene et al 2002), but only 5-10% of all cases have been estimated to have a dominant inheritance (Easton and Peto 1990, Eeles 1999). Two key genes involved in hereditary breast cancer are BRCA1 and BRCA2 (Miki et al 1994, Wooster et al 1995). Genetic testing is available at many cancer genetics clinics in the western world, and women with a family history of breast cancer can undergo genetic testing for mutations in BRCA1 and BRCA2 as part of genetic counselling. For cases with dominant inheritance or proven BRCA mutation, a special monitoring program is offered for early detection with the intention to improve prognosis by intensified follow-up; selected cases may be offered the alternative of prophylactic surgery to prevent cancer.

Diagnosis of primary breast cancer

Since the introduction of general mammography screening for breast cancer in Sweden, the majority of cases have been detected at an earlier stage (Kerlikowske et al 1995, Nystrom et al 2002). As a consequence, there has been an increased use of surgical breast-conserving procedures. Breast cancer is investigated by three complementary methods, the so-called "triple diagnostics": clinical examination, radiological examination including mammography and/or ultrasound, and needle biopsy of the breast lump. In case of uncertainty, further examinations include a core or excision biopsy (Hermansen et al 1987, Vetto et al 1995).

Prognostic and predictive factors in early breast cancer

Early breast cancer is staged according to the TNM system (WHO), which takes into account tumour size, lymph node status, and absence or presence of distant metastases. Tumour size and number of metastatic lymph nodes are both strong prognostic factors used for selection of adjuvant treatment. Grade of malignancy and the proportion of proliferating tumour cells are frequently used as surrogate predictors of efficacy of cytotoxic agents. Vascular invasion and young age also imply an unfavourable prognosis (Elston et al 1991, Cianfrocca et al 2004, Goldhirsch et al 2007, Harris et al 2007) In contrast; oestrogen and/or progesterone receptors are predictive of response to endocrine treatment. On average, approximately 70% of all tumours are receptor-positive; this proportion is lower in premenopausal cases and higher in postmenopausal cases (EBCTCG 2005, Goldhirsch et al 2007). Overexpression of HER2, one of four membrane-located receptors for binding of different growth factors, characterizes a subgroup representing approximately 15% of breast tumours with a higher proliferation and an increased risk of early

recurrence. The incidence of HER2 overexpression is even higher (approximately 30%) in locally advanced and metastatic breast cancer (Slamon et al 1987) Women with HER2-overexpressing cancer are treated with trastuzumab, an antibody targeted against the HER2 receptor (Joensuu et al 2006, Gianni et al 2011). Hormone receptors and HER2 are currently the only factors known to predict efficacy of a targeted treatment (EBCTCG 2005, Gianni et al 2011). There is, however, evidence for a higher efficacy of chemotherapy in tumours with high proliferation (Colozza et al 2005).

Treatment of primary breast cancer

Surgery

The most common treatment for primary breast cancer is surgery, with the choice of procedure depending on the size of the tumour. Several studies have compared breast-conserving surgery with mastectomy. Breast-conserving surgery in combination with radiotherapy is a safe alternative to mastectomy when the tumour is unifocal (Fischer et al 2002, Veronesi et al 2002). For larger or multifocal tumours, mastectomy is the preferred type of surgery. Sentinel node biopsy is standard in the absence of clinical signs of axillary metastases. In case of axillary metastases detected by either palpation or sentinel node biopsy, axillary dissection is the treatment of choice.

Adjuvant therapy

The aim of adjuvant treatment is to reduce the risk of local relapse and distant metastases after the primary tumour is radically removed. Postoperative treatment includes chemotherapy, endocrine treatment, the targeted antibody trastuzumab, and radiotherapy of the breast or chest wall and, eventually, regional lymph nodes. In patients with large tumours or metastasis in axillary or supra/infraclavicular lymph nodes, primary medical treatment before operation may be considered in order to reduce tumour size. The type of treatment depends on the characteristics of the tumour. Data from clinical trials have confirmed that preoperative chemotherapy does not impair prognosis compared to postoperative treatment (Mieog et al 2007).

Chemotherapy in the adjuvant setting

Adjuvant chemotherapy reduces the risk of relapse in breast cancer. The relative improvement is equal for all patients, but in absolute numbers, patients with a high risk of relapse gain a higher

benefit from chemotherapy. Chemotherapy is the standard choice of treatment in patients with receptor-negative or larger tumours with or without lymph node metastases. Numerous different chemotherapy regimens for treatment of primary breast cancer have been investigated. The most common drugs are anthracyclines, taxanes, 5-Fu, and cyclophosphamide (Bergh et al 2001, Martin et al 2006, Hokken et al 2009, Conte et al 2004, Cassier et al 2008, Schwartzberg et al 2009). Chemotherapy regimens containing taxanes have been shown to improve both disease-free survival and overall survival (Henderson et al 2003, Mamounas et al 2005, Berry et al 2006, Jones et al 2009).

Endocrine adjuvant treatment
Patients with oestrogen and/or progesterone receptor positive breast cancer are offered endocrine treatment. Tamoxifen has long been the standard treatment. However, aromatase inhibitors have shown a higher efficacy in terms of progression-free survival but not overall survival in postmenopausal women. These drugs have a different profile of side effects. Aromatase inhibitors are used either continuously for five years, or sequentially for two to three years followed by tamoxifen for up to five years. There are also clinical data supporting prolonged use of aromatase inhibitor beyond five years in patients previously treated with tamoxifen for five years. Tamoxifen is still the standard endocrine treatment in premenopausal women (Nabholtz et al 2008)

Targeted therapy
Patients with tumours overexpressing HER2 have a poorer prognosis compared to HER2-negative patients (Slamon et al 1987). HER2 positivity is defined as intense immunohistochemical staining (3+) of the cell membrane or gene amplification apparent by *in situ* hybridization (ISH) techniques (Wolff et al 2007). In Sweden, all tumours with HER2 2+ or 3+ by immunohistochemistry are routinely also tested by ISH . Approximately 15-30 % of all breast cancers overexpress HER2 (Slamon et al 1989, Owens et al 2004, Dent et al 2006). Several large clinical trials have shown that adjuvant treatment with trastuzumab (Herceptin®), a monoclonal antibody with high specificity to HER2, reduces the risk of DFS and OS in patients with HER2-positive tumours (Joensuu et al 2006, Smith et al 2007, Piccart et al 2005, Gianni et al 2011). Standard treatment for women with HER2-positive breast cancer is chemotherapy containing anthracyclines and taxanes, and one year of treatment with trastuzumab. Some other

targets of treatment are currently being investigated in clinical trials, but are not in use as standard adjuvant treatment.

Radiotherapy

Radiotherapy reduces the risk of local recurrence and also improves survival (Clarke et al 2005). Patients who undergo breast-conserving surgery have a higher risk of local recurrence without radiotherapy, and so these patients are offered radiotherapy to the breast. Radiotherapy to the chest wall after mastectomy is recommended if the tumor is not radically removed. Radiotherapy is also offered to the chest wall and lymph nodes if the tumor is metastatic to the lymph node. Fisher et al 1995, Veronesi et al 1995, Clarke et al 2005)

Treatment of metastatic breast cancer

Metastatic breast cancer is not curable. The goals of treatment are disease control and prolongation of survival. Palliative interventions include radiotherapy and adequate medication with analgesics and other supportive measures. Treatment options are similar to those used in primary breast cancer. However, the most effective cytotoxic drugs, anthracyclines and taxanes, have usually already been used in adjuvant treatment. They may be used again if the disease-free interval is long enough to exclude the risk of primary resistance to these drugs. Efficacy of treatment in terms of response and progression-free survival is considerably higher in early metastatic disease, and decreases with subsequent regimens. Therefore, it is of great importance to select effective treatment alternatives for use in early metastatic disease. Depending on the clinical course and the site of metastases, patients with hormone sensitive breast cancer can be offered endocrine therapy. In general, patients who relapse with receptor-negative breast cancer or on adjuvant endocrine therapy should be offered chemotherapy as first-line treatment (Fossati et al 1998). The choice of appropriate cytotoxic treatment depends on the patient's general condition, symptoms, and site of metastases. Besides anthracyclines and taxanes, the drugs used in the metastatic setting include capecitabine and vinorelbine, as well as trastuzumab and lapatinib in the case of HER2-positive breast cancer (Gomez et al 2008, Bontenbal et al 2005, Cardoso et al 2009, Welt et al 2005, Schwartzberg et al 2009, Seidman et al 2002, Slamon 2001, Marty 2005, Nabholtz JM et al 1999, O´Shaughnessy J et al 2002). The most common drugs in first-line treatment with chemotherapy are anthracyclines and taxanes (Ghersi et al 2003, Bontenbal et al 2005, Cardoso et al 2009). Capecitabine in combination with docetaxel has

shown prolonged PFS and OS compared with docetaxel alone (O´Shaughnessy et al 2002). In patients with HER2-positive breast cancer, a recently published study showed no difference in outcome between vinorelbine and docetaxel combined with trastuzumab (Andersson et al 2011). Lapatinib has shown efficacy when combined with trastuzumab (Blackwell et al 2010) and in combination with capecitabine (Cameron et al 2008).

Bisphosphonate reduces the risk of skeletal complications, and is a standard treatment in patients with bone metastases (Pavlakis et al 2005, Hatoum et al 2008). Radiotherapy is frequently used for palliation of symptomatic bone metastases, but also for management of other symptomatic metastases (Kaasa et al 2006, Gerber et al 2010).

Post-recurrence survival, sites of metastasis

The risk of recurrence from breast cancer is highest within the first five years after primary surgery, especially during the first and second years (Saphner et al 1996, Fischer et al 2002, Elder et al 2006). The prognosis of patients with metastatic breast cancer is poor, with an estimated five-year survival of only 21% (Hayat et al 2007). Other authors report median survival rates ranging from 18 to 34 months (Ataly 2003, Chang et al 2003, Marty et al 2005, Nistico et al 2006, Er et al 2008). Approximately 6-10 % of diagnosed breast cancer patients have metastatic disease at diagnosis, and approximately 25-30% will eventually develop metastatic disease (O´Shaughnessy et al 2005). Common sites of distant metastasis are bone, lung, and liver (Zinger et al 1987, Kamby et al 1987, Carty et al 1995, Diaz Canton et al 1998, Nistico et al 2006). Bone is the most frequent and first metastatic site (Sherry et al 1986, Kamby et al 1987, Solomayer et al 2000, Elder et al 2006). A study comparing clinical and autopsy data showed that 69% of all patients with known metastatic disease had bone metastases by the time of death (Kamby et al 1990). The site of first recurrence has an impact on the length of survival. Patients with bone metastases as the first and only site of relapse have a longer median survival than patients with visceral metastases, especially those located in the liver (Solomayer et al 2000, Elder et al 2006). However, patients with liver metastases alone have a longer life expectancy than patients who also have metastases at other sites (Ataly et al 2003, Er et al 2008). Elder et al. found that when relapse occurred, in 79% of cases it was within the first five years. They also reported five-year survival rates of 16% for patients with bone metastases, 12% for patients with lung metastases, and zero for patients with liver metastases. These survival results are comparable to those published by Solomayer et al., who found a median post-recurrence survival of 24 months for

patients with skeletal metastases *versus* 12 months for those with visceral metastases (Solomayer et al 2000).

Prognostic and predictive factors in metastatic disease

The location of metastatic sites at detection of recurrence and the grade of dissemination are important factors, with a strong impact on survival, while the stage of the early cancer is of limited value. The length of the disease-free interval reflects the biological regrowth rate of the tumour after primary treatment. Together with the performance status before start of treatment, this combined information is generally used for the clinical therapeutic approach. Previous adjuvant chemotherapy appears to impair the prospects for chemotherapy. Similarly, recurrence during adjuvant endocrine treatment is a marker for reduced sensitivity to hormonal treatment in metastatic disease. However, ER, PgR, and HER2 status are valuable predictive factors in disseminated disease. In addition, HRQoL variables (physical functioning, pain, and loss of appetite) have been identified as independent prognostic variables in a number of studies (Efficace et al 2004, Quinten et al 2009) HRQoL at diagnosis has also been shown to be an independent prognostic factor, though only in one study (Grøenvold et al 2007)

Toxicity during chemotherapy

The most common side effects of chemotherapy regimens containing anthracyclines, taxanes, capecitabine, or vinorelbine are nausea, vomiting, fatigue, cardiac toxicity (congestive heart failure), mucositis, alopecia, loss of appetite, taste disturbance, diarrhoea, constipation, sensory neuropathy, myalgia, fluid retention, febrile neutropenia, haematological toxicity, nail changes, hand-foot syndrome, insomnia, and hypersensitive reactions (Marty et al 2005, Ghersi et al 2005, Martin et al 2006, Cassier et al 2008, Hackbarth et al 2008, Seidman et al 2002, Ryberg et al 2008, Albain et al 2008, Schwartzberg et al 2009, Sparano et al 2008 , Mauri et al 2010). The grade of toxicity depends on the type of chemotherapy, the doses, and the duration of treatment.

Single nucleotide polymorphism (SNP) and drug metabolism

A single nucleotide polymorphism is defined as a variation of one nucleotide in which one allele is present in more than 1% of the studied population. It is estimated that the human genome contains approximately 10 million SNPs, of which 3.1 million have been validated via the HapMap project (Frazer et al 2007). SNPs are likely to play a dominant role in drug metabolism,

which in turn affects both the efficacy and intensity of the drugs' side effects. There are studies showing that SNPs may be responsible for serious side effects related to chemotherapy (Johnson et al 1999, Sissung et al 2006, Ribelles et al 2008, Fasching et al 2008). Multiple SNPs associated with the metabolism of certain compounds have been reported previously, along with their impact on the efficacy and toxicity of the treatment. The SNP analyses in Study III focused on the metabolism of the cytotoxic drugs involved in the TEX study.

TEX study

The TEX trial was an open randomized multicentre phase III study of first-line chemotherapy for metastatic breast cancer. Its aim was to compare the efficacy of different chemotherapy combinations in terms of progression-free survival (PFS, primary endpoint), objective response, overall survival, toxicity, and quality of life. Originally, three chemotherapy combinations were investigated: FEC (fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, and cyclophosphamide 600 mg/m^2), ET (epirubicin 75mg/m^2 and paclitaxel 175mg/m^2), and TEX (epirubicin 75mg/m^2, paclitaxel 155mg/m^2, and capecitabine 825mg/m^2). The FEC arm was designated as standard treatment. However, since publications during the start phase of the trial showed superiority of combinations including taxanes (Jassem et al 2001, Nabholtz et al 2003), the TEX trial group took the decision to phase out the FEC option. Seventeen patients received FEC and were not included in the analyses regarding outcome. From December 2002 to June 2007, a total of 308 patients from ten Swedish hospitals were randomized in the trial: 17 patients to FEC, 143 patients to ET, and 144 patients to TEX. Four patients were randomized but excluded for various reasons and without having received the study treatment. The trial was approved by the ethics committees at the participating centres. The inclusion criteria were: women $\geq$18 years, with morphologically confirmed locally advanced or distant metastatic breast cancer with measurable or evaluable lesions who may or may not have received adjuvant treatment. The exclusion criteria were: interval less than one year since termination of adjuvant therapy if previous treatment with one of the investigational drugs, cumulative doses of epirubicin exceeding 550 mg/m^2 or doxorubicin exceeding 350 mg/m^2, HER2 overexpression, previous chemotherapy for metastatic disease, previous other malignancy within five years, known brain metastases, and diseases which could jeopardize adequate study treatment. Treatment was continued until progression, occurrence of unacceptable toxicity, other medical reasons to cease treatment, or patient's request to cease. In cases with stable disease or objective response with no further improvement at repeated

evaluations, study treatment could be replaced by either endocrine treatment in cases with hormone receptor positive tumours, or, in the ET arm, by a switch to treatment with capecitabine alone. In patients with continuous response approaching maximum accumulated dose levels of epirubicin, or experiencing intolerable symptoms related to paclitaxel or capecitabine, treatment continued after removal of these drug(s) until progression or other medical causes for disruption occurred. Patients who progressed after first-line treatment in the ET arm were offered capecitabine as second-line treatment upon progression. Epirubicin was given as a 30-minute infusion on day 1 followed by a 3-hour infusion with paclitaxel. In the TEX regimen, oral capecitabine was given twice daily for 14 days. The FEC treatment was given according to local guidelines. Treatment was repeated every three weeks. All patients received premedication with intravenous betamethasone, intravenous ranitidine, and oral cetirizine before start of treatment. Drug doses were adjusted individually in relation to side effects; doses were escalated stepwise in patients who did not experience significant side effects, while drugs causing toxicity were reduced. Response evaluations were performed after every third course. Disease progression was defined according to version 1.0 of the Response Evaluation Criteria in Solid Tumors (RECIST) (Therasse et al 2000). Toxicity grades were assessed and registered after each cycle, based on version 2.0 of the Common Toxicity Criteria (CTC).

Health-related quality of life (HRQoL)

The most well-known and frequently-quoted definition of health is that published by the World Health Organization (WHO) in 1946: "Health is a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" (WHO 1946). In relation to the concept of health, health status is often referred to as quality of life and quality of life is, in turn, often referred to as health-related quality of life (HRQoL) in research studies (Gill & Feinstein 1994). HRQoL includes a multidimensional construct which incorporates the psychological, social, and physical functioning that is affected by treatment or disease (Cella et al 1990). The functional aspect includes basic daily activities such as the ability to dress, work-related activities, housework, the ability to cope at work, and spending time with family and friends to the extent desired. When measuring HRQoL, the intention is to capture both functional aspects as well as symptoms produced by the disease or its treatment (Lehman et al 1995, Aaronson et al 1993). The World Health Organization Quality of Life group (WHOQOL) defines quality of life as "an individual's perception of their position in life in the context of the culture and value

systems in which they live and in relation to their goals, expectations, standards and concerns" and states that it is "a broad ranging concept affected in a complex way by the person's psychological state, level of independence, social relationships, and their relationships to salient features of their environment" (WHOQOL group 1993b:3). According to another definition, quality of life is a multidimensional measure that theoretically incorporates all aspects of an individual's life (Bowling 2009).

Measurement of HRQoL provides information that is useful for understanding how disease and treatments affect the daily life of an individual or group of patients. It should, however, be noted that quality of life means different things to different people. Quality of life assessments are used in many disciplines, for example social science, medical science, philosophy, health economics, health promotion, and geography. There are many different ways to measure HRQoL, and a large number of instruments have been developed over the years (Coates et al 1983, Ware et al 1993, Cella et al 1993, Aaronson et al 1993). HRQoL instruments (assessments) should meet basic properties such as validity, reliability, repeatability, responsiveness, and sensitivity (Fayers & Machin 2009).

Validity, or authenticity, means that the instrument measures what it is intended to measure and reliability refers to the precision of the instrument and its repeatability. A test with high reliability provides the same results from several tests. One common method to test reproducibility is to perform test-retest. An instruments sensitivity is the ability of a rating scale to detect and measure differences between individuals and groups and responsiveness is the ability of an instrument to detect changes in one person over time (Bowling 2009, Fayers & Machin 2009,).

HRQoL instruments

A large number of generic instruments have been developed for measuring HRQoL. Some of the instruments are intended for general use, irrespective of the patient's condition or illness. Often, these generic HRQoL instruments are also applicable to the general healthy population (Bowling 2009). Some examples of generic HRQoL instruments are given below.

The *Sickness Impact Profile (SIP)* measures perceived health status, and can be used in many types and severities of illness. The questionnaire consists of 136 items, and emphasizes the impact of health on activities and behaviour (Bergner et al 1981).

The *Nottingham Health Profile (NHP)* measures emotional, social, and physical distress. In contrast to the SIP questionnaire, which focuses on changes in the respondent's behaviour, the NHP places the focus on feelings and emotions (Hunt et al 1981).

EuroQoL (EQ-5D) is intended to be applicable over a wide range of health interventions. The instrument measures five dimensions of HRQoL, and the respondent is asked to answer five questions concerning mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents are asked to mark their own health states on a vertical visual analogue scale (VAS) from 0 – 100, ranging from the best imaginable health states to the worst imaginable health states (Brooks et al 1996).

The *Short Form (36) Health Survey (SF-36)* was developed by international collaboration, and has been widely used (Ware et al 1993, Jenkinson et al 1999). The instrument consists of 36 questions covering eight health concepts, and includes two summary measures: physical health and mental health. Physical health is divided into scales for physical functioning, physical role functioning, bodily pain, and general health. Mental health is divided into scales for vitality, social functioning, emotional functioning, role functioning, and mental health. SF-36 has been validated in Swedish, and norm values from the Swedish population have been published (Sullivan et al 1998).

The generic HRQoL instruments often fail to focus on the issues for patients with specific diseases, which have led to the development of disease-specific questionnaires (Fayers & Machin 2009). Two examples of cancer-specific HRQoL questionnaires are described below.

The *European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30)* is one of the most widely used and validated quality of life instruments in cancer populations (Aaronson et al 1993, Osoba et al 1997, Bjordal et al 2000, Garatt et al 2002). It is a cancer-specific HRQoL instrument that includes many important domains for investigation

of patients undergoing treatment (Cull et al 1997, Fayers & Bottomley 2002). The Swedish version of EORTC QLQ-C30 (version 3) has been validated (Bergman et al 1991; 1992, Sigurdsdottir et al 1993; 1996). This instrument was used in the present studies, and is described in greater detail in the Methods section.

Functional Assessment of Cancer Therapy: General (FACT-G) was developed by Cella et al. (1993) and is widely used in cancer patients. It includes a number of supplementary modules for specific tumour types, conditions, and treatments. It is also used for other diseases such as multiple sclerosis and HIV infection (Fayers & Machin 2009). The questionnaire consists of 27 items covering four dimensions of quality of life: physical well-being, social/family well-being, emotional well-being, and functional well-being (Cella et al 1993).

There are some differences between the EORTC QLQ C-30 and FACT-G. The EORTC QLQ C-30 questionnaire emphasizes clinical symptoms and ability to function, while FACT-G addresses concerns and feelings. In studies of treatment outcomes, generic instruments should be supplemented with a disease-specific questionnaire, and study-specific questions relevant to the disease may also be added. One example of a disease-specific questionnaire is the EORTC Breast Cancer Module (EORTC QLQ BR-23), which is a breast cancer specific questionnaire developed for use among patients varying in disease stage and treatment modality (Sprangers et al 1996).

AIMS

All four studies in this thesis were based on the TEX study. The overall aim of these four studies was to examine HRQoL in women with metastatic breast cancer over time during treatment with first-line chemotherapy, and to examine their psychological reactions at the time of disease progression.

Study I

The aim of Study I was to compare the effects of two treatment regimens on HRQoL at five assessment points during nine months from random assignment to treatment. Special emphasis was placed on examining differences between the treatment groups at two of these points: two months after the randomization, when side effects were expected to peak, and nine months after

randomization, when the patients were expected to have adapted to treatment.

The specific research questions were:

• Are there differences between the two treatment groups two months after randomization?

• Are there differences between the two groups nine months after randomization?

Study II

The aim of Study II was to investigate the role of HRQoL variables at randomization as independent prognostic factors for response to treatment, progression-free survival, and overall survival. The specific research questions were:

• Are HRQoL factors independent predictors for response to treatment?

• Are HRQoL factors independent predictors for progression-free survival?

• Are HRQoL factors independent predictors for overall survival?

Study III

The aim of Study III was to describe the associations between HRQoL and the results of analyzing a number of specific SNPs that may be predictors of increased toxicity of treatment. The specific research questions were:

• Is there an association between toxicity and HRQoL?

• Is there an association between toxicity and SNPs?

• Is there an association between SNPs and HRQoL?

Study IV

The aim of the interview study, Study IV, was to explore psychological reactions and coping at disease progression after first-line chemotherapy in the TEX trial. The specific research questions were:

• How did the patients react when they were informed about their disease progression?

• How did they cope with their situation after knowledge of disease progression?

METHODS

Randomization procedure

Patients who fulfilled the inclusion criteria were registered and randomized, after giving their oral and written informed consent. The form for randomization was sent to the Clinical Trial Office (CTO), Clinical Trial Unit, Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden, who then faxed it to the Oncologic Center, Sahlgrenska University Hospital, Gothenburg, Sweden for randomization. Within 24 hours, an answer was delivered to the study centre. Stratification was performed for the ten study centres, and randomization was achieved using a permuted block technique.

The FEC group was excluded after 17 patients had been included, due to new data regarding first-line taxane treatment for metastatic disease (Jassem et al 2001). These patients were excluded from Studies I–III, though four of them were included in Study IV.

Subjects

The patients were recruited between December 2002 and June 2007 from ten clinics in Sweden. The inclusion criteria in the TEX trial were women $\geq$18 years, with documented locally advanced or distant metastatic breast cancer; measurable or evaluable metastases (including those with metastases only in the bone); ECOG performance status 0-2; adequate cardiac, haematological, renal, and hepatic function; and life expectancy of at least three months. Exclusion criteria were: less than one year of disease-free interval after adjuvant therapy, previous use of any of the investigational drugs, cumulative doses of doxorubicin exceeding 350 mg/m^2 or epirubicin exceeding 550 mg/m^2, HER2/neu overexpression, previous chemotherapy for metastatic disease, previous cancer diagnosis within five years, brain metastases, or diseases which could jeopardize adequate treatment within the study.

Participants in Studies I-III were randomized to the ET or TEX group, and participants in Study IV were randomized to the FEC, ET, or TEX group.

Study I

Study I included 163 patients who responded to the EORTC QLQ C-30 and QLQ BR-23 at all five points of assessment. Two of these assessment points were of special interest; two months

after randomization, when treatment side effects were expected to be at their worst, and nine months after randomization, when the patients were expected to have either adapted to the treatment or been offered other treatment due to disease progression or toxicity. The other points of assessment were included to allow more detailed study of the effects of treatment on HRQoL over time.

Study II

Study II included 252 patients who answered the QLQ C-30 at randomization.

Study III

Study III included 185 patients who answered the QLQ C-30 at the two-month assessment and gave blood samples for the SNP analysis.

Study IV

Study IV included 20 patients with disease progression, chosen consecutively from the TEX trial between March 2006 and May 2007. A total of 22 patients were asked to participate, and 20 consented, with the other two declining due to poor general condition.

 Detailed characteristics of the participants are listed in Table 1.

Table 1. Patient characteristics.

SUBJECTS				
Total number of patient	163	252	185	20
	Paper I	Paper II	Paper III	Paper IV
Age at randomisation, mean, min-max] years				
	54[29- 74]	54.9 [29- 74]	54.7 [29- 74]	54.5 [43- 66]
ECOG at study entry				
0	115 (71)	174(69)	129(70)	16(80)
1	38 (23)	63 (25)	45(24)	3(15)
2	6 (4)	12 (5)	8(4)	1(5)
Missing	4 (2)	3 (1)	3(2)	
Metastatic site:				
Bone	101(62)	152 (60)	114(61)	12(60)
Lung	53(33)	85 (34)	57(31)	7(35)
Pleura	27(17)	43 (17)	33(18)	3(15)
Liver	61(37)	107 (43)	76(41)	12(60)
Regional/loco regional nodes	40(25)	60 (24)	51(28)	3(15)
Distant nodes	53(33)	78 (31)	56(30)	3(15)
Total number of metastatic sites, mean [SD, min-max]	2.3 [1.1 , 1-6]	2.6 [1.3, 1-7]	2.45[1.1, 1-6]	2.2 [0.8, 1-4]
Single site (1)	42(26)	56(22)	40(22)	4(20)
Multiple sites (>1)	121(74)	196 (78)	145(78)	16(80)
Time between diagnosis and randomisation, mean [SD, min-max], years	6 [5.3, 0-26]	5.8 [5.4, 0-26]	5.7 [5.3, 0-26]	6 [4,7 , 0-15]
≤2 years	37 (23)	65 (26)	51 (28)	2(10)
>2 years	126 (77)	187 (74)	134 (72)	18(90)
Time interval (months) between date of metastatic disease and date of randomisation, mean [SD, min-max]	11 [22 , 0-144]	10 [21 , 0-144]	10 [20 , 0-108]	8.5 [22 , 0-93]
Allocated treatment:				
TEX	83(51)	126 (50)	92(50)	7(35)
ET	80(49)	126 (50)	93(50)	9(45)
FEC				4(20)
ER and/or PR (primary tumor)				
Positive	125(77)	185 (73)	131(71)	17(85)
Negative	27(16)	49 (19)	39(21)	3(15)
Unknown	11(7)	18 (7)	15(8)	
Previous endocrine treatment for metastatic disease	55(34)	82(32)	62(34)	5(25)
Best response of treatment				
CR	8(5)	10 (4)	10 (5)	1(5)
PR	81(50)	117 (46)	89(48)	10(50)
SD	60(37)	83 (33)	60(32)	6(30)
PD	10(6)	29 (12)	20(11)	3(15)
NE	4(2)	13 (5)	6(3)	
Previous medical adjuvant treatment	117(72)	176(70)	131(71)	18(90)
Only Chemotherapy	27(17)	52(21)	39(21)	4(20)
Only Endocrine	36(22)	51(20)	41(22)	7(35)
Chemo + endocrine	54(33)	73(29)	51(28)	7(35)

Procedure

Studies I-III

The patients were informed about the main study (TEX) and the HRQoL assessment by the responsible physician at the same time. The information was provided both orally and in writing. After informed consent, patients received the first questionnaire from the study nurse or the physician together with a return envelope addressed to the Clinical Trial Unit, Department of Oncology, Karolinska University Hospital. Thus, the first point of assessment was after informed consent but before randomization, and therefore before patients were told which treatment arm they would be in. The subsequent HRQoL assessment points were two, four, six, and nine months after randomization. The Clinical Trial Unit at the Department of Oncology, Karolinska University Hospital sent the questionnaires to the participants by mail, together with an information letter and a return envelope. If no reply was obtained within two weeks, one reminder was sent, but not to the patients who had not responded at the first assessment point before randomization. Patients whose disease progressed were still included in the HRQoL evaluation.

Study III - SNP

A separate informed consent was obtained from the patients who agreed to participate in the optional blood pharmacogenomic part of the TEX trial. The patients were informed orally and in writing before the blood sample were taken. A blood sample was taken from each patient in a single tube, stored at -80°C at the study centre, and then sent to the Cancer Centrum Karolinska (CCK), Karolinska Institute, Stockholm. Some of the blood samples were taken during the patients' treatment period, but the majority was taken after randomization and before start of the first cycle.

Study IV

The participants in Study IV were recruited between March 2006 and May 2007 at two clinics, located at the Sahlgrenska and Karolinska University hospitals. They were informed about the interview study by the physician both orally and in writing at the same time as they were given information about disease progression of first-line treatment. Signed informed consent was obtained from each patient before proceeding. Following consent, an appointment was scheduled for the interview. Semi-structured interviews were conducted in a private room at the outpatient

clinic and performed within one week after the patient had been informed of progression. The interviews lasted between 26 and 69 minutes (mean value 44 minutes, SD=11) and were tape-recorded and transcribed verbatim. The interviews were performed by one psychologist and one research nurse but none of the interviewers was involved in the TEX trial.

A preparatory meeting took place to discuss the interview guide and interview techniques in order to ensure consistency between the interviewers before start of data collection. After six interviews, one follow-up meeting was held to discuss the proceedings. Code numbers were used in order to avoid identifying the participants.

Instruments

The European Organization for Research and Treatment of Cancer (EORTC) was founded in 1962. Its aims are to conduct, develop, coordinate, and stimulate cancer research in Europe.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) is a HRQoL questionnaire developed by the EORTC Quality of Life Study Group to measure a range of quality of life issues relevant to cancer patients in clinical trials (Aaronson et al 1993). The original version of the questionnaire contained 42 items, but this was subsequently reduced to 36 and then 30 items. Guidelines for development of EORTC QLQ modules have been published (Sprangers et al 1993). The current version (version 3) of the EORTC QLQ-C30 was used in the present studies. It consists of 30 items comprising five function scales: physical functioning (PF) measures the capacity to perform a range of daily activities, emotional functioning (EF) measures psychological distress, social functioning (SF) measures perceived disruption of family life and social contacts, role functioning (RF) measures the patient's ability to perform their ordinary work or household activities, and cognitive functioning (CF) measures deterioration of memory and/or concentration. The questionnaire also includes three symptom scales: fatigue (FA), nausea/vomiting (NV), and pain (PA), and six single items: dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhoea (DI), and financial difficulties (FI). The last two items assess global health and overall quality of life. Most items are responded to on a four-point scale: 1 (not at all), 2 (a little), 3 (quite a bit), and 4 (very much). Global health and overall quality of life are responded to on a seven-point scale ranging from 1 (very poor) to 7 (excellent). (Aaronson 1988, Schwartz et al 2002).

The EORTC QLQ Breast Cancer Module (QLQ BR-23) is a breast cancer specific questionnaire developed for use among patients varying in disease stage and treatment modality (e.g. surgery, radiotherapy, chemotherapy, and hormonal treatment) (Sprangers et al 1996). It comprises 23 items divided into four functioning scales: body image (BRBI), sexual functioning (BRSEF), sexual satisfaction/enjoyment (BROSE), and future perspective (BRFU); and four symptom scales: systemic therapy side effects (BRST), breast symptoms (BRBS), arm symptoms (BRAS), and being upset by hair loss (BRHL). The questionnaire has been validated in an international study (Sprangers et al 1996). The items are responded to in the same four categories as the majority of the items in the EORTC QLQ-C30.

Studies I–III used the EORTC QLQ-C30, and Study I also used three subscales from EORTC-BR23: body image (BRBI), future perspective (BRFU), and systemic therapy side effects (BRST).

Interview guide

The interviews followed guidelines which were developed by the authors through careful consideration of the aim of the study and reviews of relevant literature. The semi-structured interview guide is presented in Table 2. All areas were addressed, but the order and formulation of the questions varied.

Table 2: Psychological reactions to disease progression after first line therapy among women with metastatic breast cancer.

Areas that were addressed during the interview:

- What information has the patient received (ask her to describe with her own words)?
- How did the patient react when she received the information about the disease?
- Opinions about the information
- Did she have anyone with her when she received the information?
- How did people close to her react?
- How does the patient feel physically and mentally after the information?
- How does it affect her daily life?
- Thoughts: How does the patient view her situation now and in the future?
- What worries the patient most?
- How much does she worry, what consequences does the worry have?
- What does the patient think would make things easier in this situation (information earlier, preparation for the visit, to bring someone along, possibilities for contact after the visit, etc.)?
- Intellectual/emotional understanding?

Toxicity, response evaluation, and clinical data

After each cycle, the patient's toxicity was assessed and registered according to version 2.0 of the Common Toxicity Criteria (CTC) (http://ctep.cancer.gov/reporting/ctc.html 1999).

Evaluation of tumour response was performed every third cycle. The response was evaluated according to version 1.0 of RECIST (Therasse et al 2000). Patients with only bone metastasis were evaluated according to the WHO criteria (WHO).

Clinical data regarding medical history were collected at baseline.

Analyses

Statistical methods

Versions 15.0 and 16.0 of the SPSS software package were used for some of the descriptive statistical analyses of the socio-demographic and medical variables in Studies I-III. All analyses in Studies I-III were performed according to the "intention-to-treat" principle.

EORTC QLQ scoring in Studies I-III

Data from the QLQ-C30 and BR-23 questionnaires were treated according to the EORTC scoring manual (Fayers et al 2001). All items were linearly transformed to functioning or symptom scales ranging from 0 to 100. When there were missing items within some of the scales, the scores were calculated by using data from other items in that scale, as long as at least half of the items in the scales had been completed. High scores on the functional and global quality of life scales represent high levels of functioning and quality of life, and high scores on the symptom scales represent high levels of symptoms (Aaronson et al 1993). The expected mean values for all QLQ-C30 subscales were calculated using age-specific normative mean reference scale scores from the Swedish population (Michelsen et al 2000).

Clinical relevance:

 In the interpretation of the HRQoL scores, a difference of ≥ 5 points on the 0–100 scale was considered clinically important. Differences of 5-9 points were considered small, differences of 10-20 as moderate, and differences of >20 as large (Osoba et al 1998).

Study I

Linear regression models were used to study the effect of treatment over time on each of the HRQoL subscales between the two treatment groups. The statistical significance was set to 0.01, because of multiple testing. The results are presented as mean differences together with 99% confidence intervals. A linear mixed model was used to study the interactions between the treatment groups and time, using all evaluable longitudinal data.

Study II

Unconditional logistic regression was used to analyze the effect of HRQoL variables on response. The results are presented as odds ratios (ORs) together with 99% confidence intervals. Proportional hazards regression was used to analyze the effect of HRQoL variables on time to

event, with both progression and death considered as events. The results are presented as hazard ratios (HRs) together with 99% confidence intervals. A stepwise variable selection procedure using backward elimination was used to identify the strongest independent HRQoL variables for response and survival. The clinical factors included in the stepwise models were age at recurrence, performance status (ECOG), metastatic site, number of sites involved, and date of diagnosis. A bootstrap resampling procedure was used to assess replication stability of the stepwise model. This technique generates a number of samples (1000) by random sampling with replacement from the original dataset. All samples had the same size as the original data. Due to multiple testing, the level of statistical significance was set to 0.01 to avoid type I errors. The frequency of inclusion is indicative of the prognostic importance of the variables.

Paper III

To analyze the relationship between specific SNPs and toxicity, logistic regression was used with an additive model (dd = 0, DD = 1, and Dd = 2, where D = minor allele and d = major allele). The results are presented as odds ratios (ORs) with 95% confidence intervals. Linear regression was used to analyze the relationship between toxicity and HRQoL, with adjustment made for treatment, response, and baseline HRQoL variables.
All of the statistical analysis was performed using the R package (http://www.r-project.org/). No adjustment was made for multiple testing, and the level of statistical significance was set to 0.05.

Content analysis

Content analysis was originally developed for the analysis of quantitative data. Systematic analysis of text was used by the church as early as the 17th century, but the term "content analysis" was not coined until 1941. Content analysis is now used in both quantitative and qualitative research, and is common in both media studies and the caring sciences. It is mostly used to detect the patterns that evolve in interviews, observations, diaries, and texts, in order to describe phenomena within the study (Graneheim & Lundman 2004, Krippendorff 2004). Content analysis is defined by Krippendorff as "a research technique for making replicable and valid inferences from texts (or other meaningful matter) to the contexts of their use" (Krippendorff 2004). The analysis enables the researcher to draw conclusions from data within the context. The data can be analyzed by formulating themes or categories (Krippendorff 2004).

The data analysis in Study IV was conducted according to content analysis. The analysis of the text was performed step by step after all the interviews had been conducted and transcribed verbatim. The first author listened to the interviews several times while simultaneously reading the transcripts, in order to make any necessary corrections and to gain an understanding of the entire context. The text was then read through several additional times with the intent of identifying issues of interest relevant to the purpose of the paper. The initial content analysis was performed by the first author, and then the analyses were discussed and finalized in a series of consensus meetings with the last author. Code words or concepts were entered in the margin of each transcript to mark the meaning units, and then the text was condensed. The condensed meaning units were analyzed, coded, compared, and sorted into sub-themes and finally themes. Similar codes were grouped together according to common elements. All codes were checked against the meaning units and the text several times; some codes and sub-themes were changed during this process.

Ethics

The trial was approved by the ethics committees for all of the participating centres and has been conducted in accordance with the declaration of Helsinki on ethical principles for medical research involving human subjects, adopted by the general assembly of the world medical association (WMA 2008).All patients were informed about the study both orally and in writing, and signed informed consent was obtained from all participants.

RESULTS

The results of Studies I–IV are summarized below.

Study I

HRQoL at baseline

At baseline, the two study groups differed significantly on 2 of the 18 HRQoL variables. Women in the ET group had lower scores on both global quality of life and physical functioning, in comparison to the TEX group.

HRQoL at the two-month assessment

We found no statistically significant differences between the patients in the two study groups regarding HRQoL two months after randomization, although there were some small clinical differences. Patients in the TEX group reported lower values on global quality of life and role and social functioning, and also seemed to have more fatigue, dyspnoea, and diarrhoea than patients in the ET group. The patients in the TEX group reported problems of small clinical significance with insomnia and emotional problems, and also better future perspectives.

HRQoL at the nine-month assessment

The patients in the TEX group reported statistically significantly higher values on global quality of life and physical functioning than the ET group at the nine-month assessment. There were also small clinical differences in favour of the patients in the TEX group regarding global quality of life, physical functioning, role functioning, emotional functioning, dyspnoea, and insomnia. Data are presenting in Table 3

Interactions between treatment and time

Interactions between the two study groups and time were found for three of the HRQoL variables: physical functioning ($p=0.015$), role functioning ($p=0.005$), and global quality of life ($p=0.003$). These results indicate that HRQoL scores differed between the ET and TEX group over time, though the differences for global quality of life and physical functioning were already apparent at baseline.

Table 3. Mean QLQ-C30 and QLQ-BR23 scale scores by treatment group at the two assessment points of primary interest.

HRQOL scale	Month	Mean scale score (SD)		Mean difference[†] from baseline (SD)		Mean difference[‡] at assessment (99% CI)	P-value
		TEX	ET	TEX	ET		
EORTC QLQ-C30:							
Global health, QL2	2	45.9 (21.3)	47.8 (24.4)	-11.4 (25.2)	-1.9 (28.8)	-4.4 (-12.1 to 3.2)	0.14
	9	60.2 (21.4)	50.0 (22.8)	2.4 (25.8)	-0.5 (27.9)	8.2 (0.1 to 16.3)	0.009
Physical functioning, PF2	2	66.6 (21.5)	67.1 (23.3)	-8.9 (23.2)	-4.2 (23.0)	-2.5 (-9.2 to 4.3)	0.34
	9	77.8 (16.1)	68.9 (22.1)	1.4 (22.8)	-3.3 (24.4)	7.4 (0.8 to 14.1)	0.004
Role functioning, RF2	2	38.9 (31.1)	45.1 (32.6)	-19.1 (39.4)	-4.6 (38.8)	-8.7 (-19.2 to 1.9)	0.034
	9	59.1 (29.9)	50.2 (32.7)	0.0 (34.8)	-1.1 (39.4)	6.2 (-4.9 to 17.3)	0.15
Emotional functioning, EF	2	71.4 (20.1)	64.3 (25.1)	8.5 (24.3)	8.6 (25.7)	4.2 (-3.1 to 11.5)	0.14
	9	71.8 (20.7)	62.1 (20.7)	9.2 (24.5)	7.3 (27.6)	6.7 (-1.7 to 15.1)	0.039
Cognitive functioning, CF	2	75.8 (24.9)	72.8 (25.6)	-4.2 (26.4)	-0.3 (21.5)	-0.9 (-8.5 to 6.8)	0.77
	9	80.4 (23.4)	74.4 (24.1)	0.4 (25.3)	3.8 (24.9)	1.7 (-6.5 to 10.0)	0.59
Social functioning, SF	2	53.6 (30.5)	56.8 (29.4)	-18.2 (30.8)	-7.0 (31.4)	-6.8 (-16.3 to 2.7)	0.064
	9	72.3 (25.5)	62.7 (29.7)	0.5 (27.9)	0.8 (33.5)	5.7 (-4.2 to 15.6)	0.13
Fatigue, FA	2	54.9 (24.6)	51.9 (27.2)	18.7 (29.6)	7.9 (29.1)	5.9 (-2.6 to 14.3)	0.072
	9	39.2 (25.0)	45.1 (28.0)	3.4 (27.7)	2.4 (30.9)	-3.2 (-12.6 to 6.2)	0.38
Nausea and vomiting, NV	2	17.3 (20.8)	14.6 (18.5)	8.0 (22.0)	4.5 (23.5)	2.9 (-3.9 to 9.6)	0.27
	9	7.4 (14.3)	8.0 (16.9)	-1.4 (19.7)	-1.5 (23.8)	-0.6 (-6.6 to 5.5)	0.81
Pain, PA	2	28.7 (30.2)	31.2 (28.8)	-2.9 (31.9)	-8.6 (33.2)	0.8 (-8.7 to 10.2)	0.83
	9	25.1 (24.9)	31.2 (28.1)	-3.5 (30.8)	-8.5 (31.1)	-2.1 (-11.5 to 7.3)	0.56
Dyspnoea, DY	2	40.6 (30.8)	36.9 (30.1)	11.2 (36.2)	2.1 (35.5)	5.5 (-4.4 to 15.5)	0.15
	9	31.9 (26.6)	39.4 (31.0)	3.5 (35.9)	6.1 (37.8)	-6.6 (-17.3 to 4.1)	0.11
Insomnia, SL	2	25.2 (30.6)	35.4 (32.8)	-9.6 (34.1)	-6.0 (33.4)	-7.4 (-17.5 to 2.8)	0.061
	9	25.6 (27.7)	36.0 (30.4)	-8.8 (33.8)	-6.4 (34.2)	-7.7 (-18.2 to 2.9)	0.060
Appetite loss, AP	2	29.4 (31.5)	26.2 (30.2)	7.9 (40.1)	-2.7 (36.4)	4.8 (-5.8 to 15.4)	0.24
	9	16.7 (26.7)	22.3 (30.6)	-5.0 (37.5)	-4.6 (38.9)	-4.9 (-15.9 to 6.1)	0.25
Constipation, CO	2	26.7 (31.1)	28.9 (36.8)	13.9 (33.6)	10.7 (39.3)	-0.1 (-11.5 to 11.3)	0.98
	9	12.1 (21.2)	18.2 (31.9)	1.4 (25.5)	0.0 (35.0)	-3.1 (-13.2 to 6.6)	0.38
Diarrhoea, DI	2	18.3 (27.4)	14.0 (23.9)	9.8 (30.9)	3.6 (22.1)	5.1 (-3.5 to 13.7)	0.12
	9	10.2 (20.1)	10.6 (17.9)	1.4 (22.8)	0.0 (22.6)	0.1 (-7.0 to 7.2)	0.98
Financial difficulties, FI	2	23.6 (30.4)	20.0 (30.0)	4.7 (27.0)	3.1 (17.4)	2.1 (-5.5 to 9.6)	0.48
	9	26.0 (31.2)	17.6 (27.8)	5.9 (26.6)	1.2 (18.3)	5.7 (-2.5 to 14.0)	0.072
EORTC QLQ-BR23:							
Body image, BRBI	2	60.6 (28.8)	58.6 (30.9)	-16.4 (24.5)	-15.7 (26.5)	0.1 (-8.7 to 9.0)	0.97
	9	66.1 (29.7)	63.0 (29.3)	-11.0 (26.2)	-12.8 (23.9)	2.4 (-7.2 to 12.0)	0.52
Future perspective, BRFU	2	37.9 (31.9)	32.1 (29.4)	10.7 (30.0)	5.9 (30.0)	6.0 (-3.5 to 15.5)	0.10
	9	40.8 (33.6)	35.6 (30.2)	13.8 (35.3)	11.8 (31.2)	4.7 (-6.9 to 16.3)	0.29
Systemic therapy side effects, BRST	2	42.5 (16.9)	40.2 (18.2)	25.7 (17.4)	20.1 (18.1)	3.5 (-2.4 to 9.4)	0.12
	9	25.1 (14.9)	27.2 (17.3)	9.3 (15.7)	6.6 (19.7)	-0.6 (-6.7 to 5.5)	0.81

[†]Within group difference. [‡]Between group difference controlling for baseline.

High score on functional scales indicate high level of functioning
High score on the symptom scales indicate high level of symptoms

Study II

Both univariate and multivariate analyses were performed. The clinical conditions included in the multivariate analysis were age, number of metastases (1 vs. $\geq$ 2), ECOG (1 vs. 2), time between primary diagnosis and randomization date (< 2 years vs. $\geq$ 2 years), and treatment arm (ET vs. TEX).

Survival

In the univariate analysis, several HRQoL variables (global health, physical functioning, role functioning, fatigue, and pain) were statistically significantly associated with prolonged survival. In the multivariate analysis, only fatigue remained statistically significant.

Data are presenting in Table 4.

Progression-free survival (PFS)

Physical functioning, role functioning, fatigue, pain, dyspnoea, and appetite loss were all statistically significantly associated with PFS in the univariate analysis. No statistically significant associations appeared in the multivariate analysis; the variables with the closest association with PFS were fatigue (p= 0.044) and loss of appetite (p= 0.022).

Data are presenting in Table 5.

Response to treatment

Global health, physical functioning, role functioning, social functioning, fatigue, pain, nausea/vomiting, and loss of appetite were significantly related to treatment response in the univariate analysis. Role functioning, social functioning, fatigue, and appetite loss remained statistically significant in the multivariate analysis.

Data are presenting in Table 6.

Table 4. Univariate and Multivariate Prognostic Factor Analysis for Time to Death.

Variable and coding	Univariate		Multivariate[a]		Backward elimination[b]		Bootstrap[c]
	HR (99% CI)	P[d]	HR (99% CI)	P[d]	HR (99% CI)	P[d]	Inclusion %
Global Health, QL2	0.92 (0.85 to 0.99)	0.005	0.95 (0.88 to 1.04)	0.14			9.0
Physical functioning, PF2	0.92 (0.86 to 0.99)	0.002	0.98 (0.89 to 1.08)	0.66			44.9
Role functioning, RF2	0.94 (0.89 to 0.99)	0.002	0.97 (0.91 to 1.03)	0.16			5.6
Emotional functioning, EF	1.01 (0.93 to 1.09)	0.73	1.02 (0.94 to 1.11)	0.49			13.8
Cognitive functioning, CF	1.01 (0.94 to 1.09)	0.68	1.03 (0.95 to 1.12)	0.37			44.4
Social functioning, SF	0.96 (0.90 to 1.02)	0.090	1.00 (0.94 to 1.07)	0.96			7.3
Fatigue, FA	1.12 (1.04 to 1.20)	<0.001	1.09 (1.01 to 1.18)	0.003	1.09 (1.01 to 1.18)	0.004	76.7
Nausea and vomiting, NV	1.07 (0.96 to 1.18)	0.12	1.01 (0.90 to 1.13)	0.82			12.5
Pain, PA	1.08 (1.02 to 1.15)	0.001	1.06 (0.99 to 1.13)	0.029			20.5
Dyspnoea, DY	1.05 (1.00 to 1.12)	0.018	1.01 (0.95 to 1.08)	0.66			5.9
Insomnia, SL	1.00 (0.94 to 1.06)	0.98	1.01 (0.95 to 1.08)	0.67			3.5
Appetite loss, AP	1.05 (0.99 to 1.11)	0.040	1.03 (0.97 to 1.10)	0.25			4.0
Constipation, CO	1.04 (0.98 to 1.11)	0.097	1.01 (0.94 to 1.08)	0.68			5.9
Diarrhoea, DI	1.00 (0.90 to 1.11)	0.95	0.99 (0.89 to 1.09)	0.78			3.2
Financial difficulties, FI	1.02 (0.95 to 1.08)	0.53	1.02 (0.96 to 1.09)	0.42			3.1

Abbreviations: HR, hazard ratio; CI, confidence interval; HRQoL, health related quality of life.

Note: HRs for HRQoL variables refers to a 10 unit increase in scale score. Effects estimated using **proportional hazards regression**.

[a]Each of the HRQoL variables – ignoring the other HRQoL variables - are adjusted for the predefined clinical variables age (continuous), number of metastatic sites (>2, 1), ECOG (≥2, 1), time between diagnosis and randomisation (≥2 yrs, <2 yrs) and treatment (TEX, ET).

[b]Stepwise model with backward-selection search. All clinical variables are forced to be included in the model and only HRQoL variables with significance levels < 0.01 remains in the final model. Estimation based on observations with non-missing values for all specified variables.

[c]To assess the replication stability of the Stepwise model a bootstrap resampling procedure proposed by Sauerbrei at al was used. This technique generates a number of samples (1000) each of the same size as the original data, by random sampling with replacement from the original data set. The frequency of inclusion are indicative for the prognostic importance of the factors.

[d]P-value from Wald test.

Table 5. Univariate and Multivariate Prognostic Factor Analysis for Progression-free survival or Death.

Variable and coding	Unadjusted		Adjusted[a]		Stepwise[b] [backward, p=0.01]		Bootstrap[c]
	HR (99% CI)	p	HR (99% CI)	p	HR (99% CI)	p	Inclusion %
Global Health, QL2	0.94 (0.87 to 1.00)	0.016	0.98 (0.91 to 1.05)	0.42			6.5
Physical functioning, PF2	0.90 (0.85 to 0.97)	<0.001	0.97 (0.89 to 1.05)	0.28			3.6
Role functioning, RF2	0.94 (0.89 to 0.98)	0.001	0.97 (0.92 to 1.03)	0.20			6.9
Emotional functioning, EF	1.01 (0.94 to 1.09)	0.66	1.03 (0.96 to 1.11)	0.32			17.2
Cognitive functioning, CF	1.00 (0.93 to 1.08)	0.93	1.01 (0.94 to 1.10)	0.66			4.3
Social functioning, SF	0.97 (0.91 to 1.02)	0.13	1.01 (0.94 to 1.08)	0.77			8.2
Fatigue, FA	1.08 (1.02 to 1.15)	0.001	1.06 (0.99 to 1.13)	0.044			18.4
Nausea and vomiting, NV	1.09 (0.99 to 1.20)	0.021	1.06 (0.96 to 1.17)	0.16			10.6
Pain, PA	1.06 (1.01 to 1.12)	0.003	1.03 (0.97 to 1.09)	0.28			3.8
Dyspnoea, DY	1.07 (1.01 to 1.12)	0.002	1.03 (0.97 to 1.09)	0.26			2.7
Insomnia, SL	0.99 (0.93 to 1.04)	0.51	1.00 (0.94 to 1.06)	0.94			3.7
Appetite loss, AP	1.06 (1.00 to 1.12)	0.010	1.05 (0.99 to 1.12)	0.022			25.3
Constipation, CO	1.04 (0.98 to 1.10)	0.097	1.01 (0.95 to 1.08)	0.70			1.4
Diarrhoea, DI	1.02 (0.93 to 1.12)	0.62	1.02 (0.93 to 1.11)	0.62			2.2
Financial difficulties, DI	0.99 (0.94 to 1.05)	0.67	1.01 (0.94 to 1.07)	0.85			1.9

Note: HRs for HRQoL variables refers to a 10 unit increase in scale score.

Abbreviations: HR, hazard ratio; CI, confidence interval; HRQoL, health related quality of life.

[a]Each of the HRQoL variables – ignoring the other HRQoL variables - are adjusted for the clinical variables age, number of metastatic sites ($\geq$2, 1), ECOG ($\geq$2, 1), time between diagnosis and randomisation ($\geq$2 yrs, <2 yrs) and treatment (TEX, ET).

[b]Stepwise model with backward-selection search. All clinical variables are forced to be included in the model and only HRQoL variables with significance levels < 0.01 remains in the final model.

[c]To assess the replication stability of the Stepwise model a bootstrap resampling procedure proposed by Sauerbrei at al was used. This technique generates a number of samples (1000) each of the same size as the original data, by random sampling with replacement from the original data set. The frequency of inclusion are indicative for the prognostic importance of the factors.

Table 6.Univariate and Multivariate Prognostic Factor Analysis for Response.

Variable and coding	Univariate		Multivariate[a]		Backward elimination[b]		Bootstrap[c]
	OR (99% CI)	P[d]	OR (99% CI)	P[d]	OR (99% CI)	P[d]	Inclusion %
Global Health, QL2	0.80 (0.67 to 0.97)	0.003	0.82 (0.66 to 1.02)	0.017			5.0
Physical functioning, PF2	0.83 (0.70 to 0.98)	0.004	0.86 (0.66 1.07)	0.072			6.3
Role functioning, RF2	0.84 (0.74 to 0.96)	0.001	0.84 (0.72 to 0.98)	0.003			24.7
Emotional functioning, EF	0.93 (0.78 to 1.10)	0.25	0.91 (0.75 to 1.09)	0.16			3.4
Cognitive functioning, CF	0.95 (0.80 to 1.13)	0.47	0.93 (0.77 to 1.13)	0.35			5.5
Social functioning, SF	0.85 (0.73 to 0.98)	0.003	0.84 (0.71 to 0.99)	0.005			23.3
Fatigue, FA	1.24 (1.06 to 1.45)	<0.001	1.23 (1.03 to 1.47)	0.002			17.0
Nausea and vomiting, NV	1.29 (1.04 to 1.59)	0.002	1.29 (1.01 to 1.64)	0.007			27.1
Pain, PA	1.15 (1.01 to 1.32)	0.006	1.15 (0.98 to 1.35)	0.025			4.2
Dyspnoea, DY	1.01 (0.88 to 1.15)	0.93	0.95 (0.81 to 1.12)	0.43			49.4
Insomnia, SL	0.96 (0.83 to 1.11)	0.46	0.98 (0.84 to 1.15)	0.77			13.6
Appetite loss, AP	1.22 (1.07 to 1.40)	<0.001	1.22 (1.05 to 1.41)	0.001	1.20 (1.03 to 1.40)	0.002	32.0
Constipation, CO	1.07 (0.94 to 1.23)	0.17	1.03 (0.88 to 1.21)	0.62			11.1
Diarrhoea, DI	0.86 (0.63 to 1.16)	0.18	0.87 (0.64 to 1.18)	0.23			21.2
Financial difficulties, DI	0.86 (0.63 to 1.16)	0.18	1.04 (0.89 to 1.22)	0.53			1.6

Abbreviations: OR, odds ratio; CI, confidence interval; HRQoL, health relatet quality of life.

Note: ORs for HRQoL variables refers to a 10 unit increase in scale score. Estimates based on **unconditional logistic regression**. Response categories PD/NA coded 1 and with the base outcome category CR, PR or SD coded 0.

[a]Each of the HRQoL variables – ignoring the other HRQoL variables - are adjusted for the clinical variables age (continuous), number of metastatic sites (>2, 1), ECOG (≥2, 1), time between diagnosis and randomisation (≥2 yrs, <2 yrs) and treatment (TEX, ET).

[b]Stepwise model with backward-selection search. All clinical variables are forced to be included in the model and only HRQoL variables with significance levels < 0.01 remains in the final model. Estimation based on observations with non-missing values for all specified variables.

[c]To assess the replication stability of the Stepwise model a bootstrap resampling procedure proposed by Sauerbrei at al was used. This technique generates a number of samples (1000) each of the same size as the original data, by random sampling with replacement from the original data set. The frequency of inclusion are indicative for the prognostic importance of the factors.

Study III

SNPs and toxicity

Statistically significant associations were found between several of the specific SNPs and different types of toxicity. SNPs in genes related to paclitaxel metabolism (ABCB1 2677G>T/A, ABCB1 1236C>T, CYP3A4*1B, and CYP1B1*3) were associated with sensory neuropathy, fatigue, cardiovascular symptoms, and hand-foot syndrome. Specific SNPs in genes related to capecitabine metabolism (CES2 823C>G and RRMI 2455A>G) were associated with mucositis, gastrointestinal problems, and dyspnoea. Finally, SNPs in one gene related to epirubicin metabolism (NQO1 556C>T) were associated with diarrhoea and hypersensitivity reactions.

HRQoL and toxicity

There were statistically significant relationships between several of the HRQoL variables (global QLQ, RF, PF, CF, SF, FA, NV, AP, and CO) and toxicity (fatigue, gastrointestinal problems, and pain). The results also indicated associations between several other HRQoL variables (PA, SL, CO, DI, and NV) and toxicity (dyspnoea, cardiovascular problems, hand-foot syndrome, and diarrhoea).

SNP and HRQoL

There were no statistically significant associations between any of the analyzed SNPs and the HRQoL variables.

SNPs, toxicity, and HRQoL

Some of the specific SNPs were associated with treatment-related reported toxicity and HRQoL. One SNP related to paclitaxel metabolism (ABCB1 2677G>T/A) was associated with fatigue, which in turn correlated with global quality of life. Another paclitaxel-related SNP (CYP3A4*1B) appeared to be associated with a higher frequency of hand-foot syndrome, which in turn was related to the HRQoL variables pain and appetite loss. We also found an association between one of the capecitabine-related SNPs (RRMI 2444A>G) and gastrointestinal toxicity (constipation, vomiting, nausea, and anorexia) which showed an association with the HRQoL variables physical functioning, emotional functioning, cognitive functioning, social functioning, fatigue, and pain. Data are presenting in Table 7

Table 7. Statistical significant associations between SNPs, reported toxicity and its impact on health-related quality of life

Gene and variant	D rug	Toxicity, grade 2-4	HRQOL
*CYP1B1*3*	Paclitaxel	Cardiovascular	Appetite loss, nausea/ vomiting and diarrhea
ABCB1 1236C>T	Paclitaxel	Sensory neuropathy	No relationships
ABCB1 2677G>T/A	Paclitaxel	Sensory neuropathy	No relationships
ABCB1 2677G>T/A	Paclitaxel	Fatigue	Global quality of life, physical , role and social functioning, fatigue, nausea/vomiting, appetite loss and constipation
*CYP3A4*1B*	Paclitaxel	Hand-foot syndrome	Pain and appetite loss
CES2 823C>G	Capecitabine	Mucositis	Social functioning
RRMI 2455A>G	Capecitabine	Dyspnea	Appetite loss, nausea/ vomiting
RRMI 2455A>G	Capecitabine	Gastrointestinal	Global quality of life, physical, role, cognitive and social functioning, fatigue, nausea/ vomiting , constipation and appetite loss
NQO1 556C>T	Epirubicin	Diarrhoea	Appetite loss, diarrhoea
NQO1 556C>T	Epirubicin	Hypersensitivity	Role functioning

Study IV

Main themes and sub-themes

Before the information	Immediate after information	Life after being informed of disease progression
Perception of symptoms and signs	Emotional reactions	Future perspective
	Intellectual and emotional awareness	The need for support
	Worrying for the future	Coping
		Hope

Before the information

Several patients said that they had suspected disease progression even before seeing the doctor. They had experienced new symptoms and signs, which gave rise to premonitions of disease progression. These patients were prepared, and were not surprised when the doctor informed them about the progression. However, a few patients had not expected any particular information from the doctor, despite experiencing new physical symptoms and signs that could signify progression. A couple of patients even expected to be informed of disease regression, or at least stable disease, as they had not experienced any new symptoms or signs of disease progression.

Immediate after information

The patients described many different reactions when they were informed about their disease progression. The majority experienced sadness, disappointment, sorrow, confusion, chaos, fear,

fatigue, worry, anxiety, shock, and insomnia. Some of them experienced severe anxiety including chest pain, heart palpitations, and respiratory problems. The patients who did not expect the bad information were shocked. However, those who experienced anxiety said that they had felt worse when they were informed about the first recurrence. At this stage, they knew that the disease could become worse at any time. A few patients were not shocked, as they had understood at once. A couple of patients already felt more stable after a few days. Worry was the most common reaction. The patients were concerned about the effectiveness of the new treatment, and what would happen if it did not work. Other worries concerned their families. Some of the women also described their worries about telling their family and relatives, mainly because they were concerned that the bad news would make them sad. There were also reported concerns about the last phase of life. However, despite these worries, many of the women expressed strength to move on.

Life after being informed of disease progression

Despite the serious situation, the majority of the patients reported having a positive view of the future and the ability to look forward, though some of the women did not dare to do so. Most of the patients got support from family and friends, but two of them did not receive any support at all. Some patients had professional psychosocial support before being informed of progression, and they continued to use this support afterwards. The other patients were offered psychosocial support, but declined.

The patients reported using various strategies to cope with their illness and situation, such as seeking social support, expressing their thoughts and concerns to relatives and friends, going to church, continuing to go to work, and keeping themselves busy and active with various things. They used a number of different methods to boost their energy, such as listening to music, walking, working in the garden, reading and painting pictures, and solving crossword puzzles. The majority of the patients still had some hope left. They felt that they had a fighting spirit, and they hoped that cancer research would generate new medicines.

General discussion

Most patients with metastatic breast cancer are treated with chemotherapy at some point during their disease. Treatment intention at this stage is palliative and the aim of treatment for metastatic breast cancer is to reduce tumour-related symptoms, prolong survival and improve quality of life (Gerber B et al 2010). Health-related quality of life is an important issue in patients who have an incurable cancer, taken into account that they have a relatively short expected time to live. Many of these patients may undergo a range of different treatments that will affect them both mentally and physically. As treatment efficacy and toxicity are important factors for HRQoL it is important to study the effects of oncological treatment in patients with metastatic breast cancer. Data in the present thesis are derived for patients included in a randomized clinical trial comparing two different chemotherapy regimens, the TEX trial. In this thesis we have studied HRQoL in women with metastatic breast cancer during chemotherapy over a 9-month period. Psychological reactions at treatment failure within the TEX trial were also studied.

The discussion follows the order of the aims.

Differences between the two randomization arms (the TEX group and the ET group) at the two and nine months assessment
At the two months assessment, when side effects were expected to peak, only minor differences in HRQoL between the groups were found. However, at the nine months assessment point when the patients were expected to have adapted to treatment, the TEX-group appeared to fare better. The patients HRQoL decreased after 2 months compared with before start of treatment in both treatment groups indicating that the treatments have negative HRQoL effects, but there was no statistical difference between the groups. There were however, small clinical differences in global quality of life, role,-, social function, less fatigue, dyspnoea and diarrhoea in favour for the ET group. There might be several explanations for the fact that we did not found any statistical difference in HRQoL between the groups at the 2 months assessment. One explanation could be that the side effects did not differ between the groups, despite the addition of capecitabine in the TEX group. Another explanation may be that the dose of paclitaxel was lower in the TEX-group

due to the addition of capecitabine. A lower dose of paclitaxel in the TEX-group and dose adjustment in both treatment groups might have led to that some patients experienced less side effects, which may have resulted in reduced impact on their HRQoL. The differences between the groups in global quality of life and physical function at the 9 months assessment can be explained by a difference already apparent at randomization in favor of TEX Group. There were more patients with poor performance status (ECOG 2) in the ET group.

The role of HRQoL variables at randomization as independent prognostic factors for response to treatment, progression-free survival (PFS) and overall survival.

Fatigue appeared to be associated with overall survival and response to treatment and seems to have a prognostic value in women with advanced breast cancer. These results differ from the findings in other studies, where pain (Quinten et al 2009) and loss of appetite (Efficace et al 2004), were associated with survival. Fatigue is a common symptom in this patient population. Thus we adjusted for performance status and number of metastases in the analyses. It could not be excluded that some patients might had much fatigue and thereby received a lower dose of the treatment alternative fewer treatments, which in turn may have affected the outcome for the response to treatment and survival . We found that the loss of appetite was associated with response to treatment, and this in turn might be explained by the association between loss of appetite and fatigue found in several studies (Cheung et al 2009, Kim et al 2008). The fact that loss of appetite alone should be a prognostic factor for patients' response to treatment seems unlikely. We found an association between fatigue and loss of appetite and PFS as in concordance with the findings of other studies (Winer et al 2004, Largillier et al 2008). However we did not found any statistically significant connection between HRQoL variables and PFS. Baseline fatigue could be considered as a stratification variable when randomizing women with metastatic breast cancer in clinical trials due to the independent association between fatigue and overall survival.

Associations between HRQoL and the outcomes from analysis of the SNPs that may be predictors of increased toxicity of treatment

We found statistically significant relationships between several of the HRQoL variables and toxicity (fatigue, pain, dyspneoa, cardiovascular problems, gastrointestinal problems and skin)

Associations were also found between toxicity and SNPs, but no associations were found between HRQoL and the investigated SNP's. The fact that there should be an association between the SNPs that we have chosen to analyze and the patients HRQoL was unlikely but it is an interesting area. The analysis of SNPs of the drugs used in the TEX- trial and toxicity showed associations between specific SNPs and toxicity. Our interpretation is that there is a relationship between selected SNPs that affects drug metabolism and toxicity. Several of the toxicities from chemotherapy were associated with the patients' HRQoL. Thus, there is a connection between SNPs, toxicity and quality of life. Sensory neuropathies, fatigue and hand-foot syndrome is known side effects of paclitaxel (Tan et al 2008) and almost all patients get symptoms of sensory neuropathies at some point during their treatment. However in our study, we found no relation between sensory neuropathies and the impact on patients HRQoL. Our interpretation is that few patients experienced symptoms of sensory neuropathies already at the 2 months assessment and therefore these problems did not have impact on their HRQoL at that point of time. The purpose of paper III was to identify severe toxicity that occurs early in the treatment and sensory neuropathies did not. The reported side effects from capecitabine and epirubicin were in line of what previous studies have shown (Fasching et al 2008, Lamba et al 2007, Fagerholm et al 2008). The HRQoL variables that were associated with the toxicity of capecitabine and epirubicin were global quality of life, physical-, role, cognitive, and social: functioning, fatigue, appetite loss, nausea / vomiting, diarrhoea and constipation, results that were expected.

Psychological reactions and coping at disease progression after first line chemotherapy in the TEX trial

The result shows that many of the women suspected disease progression before getting that information. Worry was the most common reaction, and the women used a number of different strategies to deal with the situation. The majority understood and accepted their situation. Their need for professional psychosocial counselling was small. The patients felt that they might have a need for counseling at first relapse. Many reported that they felt that their first relapse was more traumatic. The patients appeared to cope with their situation by the support they had by relatives and friends and the majority of them had strategies to manage their situation. They also felt that they could rely on the healthcare professionals at the clinic. In our literature review, we couldn't find any studies that had investigated how patients with metastatic breast cancer react to disease

progression during chemotherapy. More than half of them experienced new physical symptoms that inspired premonition of disease progression. The fact that the patients suspected the disease progression due of newly symptoms is important information for health care professionals in order to help and support them in the best way. Patients' perceptions and reactions described in the interviews are in line what other studies have found among patients having their first relapse (Burgess et al 2005, Turner et al 2005, Kissane et al 2007). Our interpretation is that the patients in our study have experienced a number of situations when negative information has been given to them. They seem to adapt to the new situation faster, and to have learnt how to cope with the negative news of disease progression. They understand their situation and the seriousness of it, but despite that, they could look forward and feel hope.

Methodological considerations

Ethical considerations

All included patients were informed about the study both orally and in writing and gave their written consent to participate. Patients were also informed that they could terminate participation at any time during the study. Anonymity was achieved as the patients' data were coded with a study number.

When planning the interview study (Study IV) we were aware that this was a sensitive period in the patient's life and that there was a risk that they might be upset or feel worse emotionally after the interview. The literature review showed that the knowledge in this area was limited and we felt that it was important to find out how patients manage at this stage of their illness. We believe it was an advantage that the patients already were included in a clinical study, TEX, in which the patients were familiar with the study team and continuity was obtained. The patients were informed in a safe environment at the hospital by people they already knew well. As this procedure hopefully made them feel comfortable, it might also have made it more difficult for them to refuse participation. The patients were offered psychological counseling after the interview if they needed, but none of them were interested.

Study strengths

This study was conducted within the frame of a clinical trial, the TEX study. The physicians and nurses working in this study were dedicated, and continuity with respect to the staff was high. The TEX trial was conducted according to Good clinical practice(GCP) and it was coordinated from the Clinical Trial Unit at the Department of Oncology at the Karolinska University Hospital, and all but the first questionnaire were administered from there at specified time points, including reminders. These procedures ascertain data collection of high quality. In addition, HRQoL assessment was mandatory in the protocol. The collection of biologic material, toxicity data and HRQoL at specified time points make this study special and allows for comparisons of SNP's, toxicity and HRQoL. Another strength was that the patients were unaware to which treatment they were randomized to when they responded to the first questionnaire, which makes biases in HRQoL by knowledge of treatment arm unlikely.

Methodological considerations when using interviews and questionnaires

Although interviews have the advantage of allowing the patient to freely express emotions and opinions, interviews also have some disadvantages compared to questionnaires. Interviews could be more distressing for patients than responding to a questionnaire. They are not responding anonymously. Thus, risk of biases in the responses due to social desirability is apparent. It takes time to conduct an interview and is often time-consuming to analyze the interview data. The interview is also dependent on the skills of the interviewer. The interviews in Study IV were conducted according to an interview guide, developed specifically for this study on the basis of the literature and on our clinical experience. There is a risk that some important aspects may have been neglected. We were also concerned about possible differences between the two interviewers and that the interviews were conducted in two different departments. To minimize this bias we had both preparatory and follow-up meetings. In addition, the interviewers were trained before the interviews and a psychologist listened to the first four interviews conducted in Stockholm. One major disadvantage of written questionnaires is the possibility of low response rates. There is also a risk that someone else, not the patient, completes it. Another disadvantage is that the questionnaires used in our studies are structured instruments and allow little flexibility to the respondent with respect to response format. It is not possible to explain any points in the questions that participants might misinterpret or for the patients to add extra comments.

In Study I-III we used HRQoL questionnaires (EORTC QLQ-C30 and EORTC BR-23) that have been extensively tested for reliability and validity (Aaronson et al 1993, Osoba et al 1997, Bjordal et al 2000, Garatt et al 2002). The questionnaire were developed specifically to evaluate HRQoL in cancer patients included in clinical trials, which makes it possible to compare our results with the results of similar trials. Results of HRQoL studies might be biased if patients who do not respond to the questionnaires had poorer HRQoL. However, the response rate was high in our study.

There is always a chance of finding statistically significant differences by chance when many variables are included in the analysis, as in Study I to III. Thus the results should be interpreted with caution.

It is not possible to generalize the results from paper III as further research is needed in this area. The sample in paper IV was small and as this is an exploratory study it is not possible to generalize the results to all women in this situation. Further studies are needed to confirm or reject the reported results.

CONCLUSIONS

- When comparing HRQoL between patient in the TEX group and the ET group at the 2-months assessment, when side-effects of chemotherapy had recently appeared, patients treated with the TEX combination did far worse than those receiving ET. However, after 9 months, when the patients had adapted to treatment, the TEX group seemed to have a slightly better HRQoL. For chemotherapy regimens with small differences in response, progression-free survival, and overall survival, as has been observed in the present trial, HRQoL data provide important additional information. Our results can be used when informing the patients about the HRQoL consequences of the two regimens studied.

- We found a relationship between fatigue at baseline and response to treatment and survival. Thus, fatigue may be used as an independent prognostic factor of response to

treatment, progression-free survival and overall survival in women with metastatic breast cancer. Fatigue at baseline could be taken into consideration as a stratification variable in randomised trials for patients with metastatic breast cancer.

- Associations between several genetic polymorphisms which affect the metabolism of the drugs used in the TEX trial and side effects caused by these compounds were identified. Toxicity is also related to HRQoL, especially in terms of fatigue and pain.
- Direct associations between SNPs and HRQoL were not found. However, there is an indirect relationship between SNPs and toxicity and toxicity and HRQoL. We conclude that the relationship between HRQoL as expressed by the patients' genetic properties regarding drug metabolism are equivocal. So far as this is one of few studies of this topic, there seems to be limited information on the connection between HRQoL described patient experience and drug metabolism explained by SNP analyses. More studies are needed in this area.
- Patients with disseminated breast cancer who progress during treatment seems to have resources to deal with the new situation and to find hope. Interviews reveal that the majority of the patients had suspected disease progression due to experience of new signs and symptoms before detection of objective signs of progression and most of the women responded with acceptance

- There were no needs of professional psychosocial support expressed.

Clinical implication

- Knowledge about HRQoL in the two treatment arms at different time points can be used when informing the patients about what to expect during treatment. This information can also be of help when choosing between the treatments.
- Fatigue before start of treatment has, in this and in other studies, been identified as an independent prognostic variable for response to treatment, progression-free survival and overall survival in women with metastatic breast cancer. Thus, it is important to identify patients with fatigue, investigate the underlying factors and to treat the fatigue. Fatigue is

an underestimated problem among cancer patients and it is important that health care personal ask the patients about fatigue.

- Fatigue may be considered to be use as a stratification variable in clinical trials among patients with metastatic breast cancer.

- Knowledge of the correlations between HRQoL and toxicity, specific SNPs and toxicity and correlation between SNPs, toxicity and its association with HRQoL can influence the choice of chemotherapy in this patient population, depending on the treatment, the toxicity profile and its impact on patients' HRQoL.

- Genetic markers related to certain severe side effects may enable identification of patients with high risk of drug-specific toxicity and, thereby, a worsened quality of life if exposed to these treatments.

- There were no needs for professional psychosocial support at the time of information about progression, but the patients suggested that counselling could be offered at first relapse. The frame of the TEX trial provided patients with high continuity with regards to doctor and nurses, and regular contacts with medical staff. Thus, it is possible that this context helped them to cope with the situation and was an important facilitator in handling the bad news.

Svensk sammanfattning av avhandlingen

Denna avhandling innehåller fyra delarbeten som handlar om hälsorelaterad livskvalitet (HRQoL) hos kvinnor med metastaserande bröstcancer. Det övergripande syftet med avhandlingen är att studera HRQoL och psykologiska reaktioner hos kvinnor med metastaserande bröstcancer som genomgår cytostatikabehandling. Livskvalitet som prognostisk faktor för tumörrespons, progressionsfri överlevnad och total överlevnad har också undersökts, liksom sambandet mellan HRQoL, biverkningar och utvalda biologiska variationer (SNP's). Patientmaterialet i avhandlingen utgörs av kvinnor som ingick i en randomiserad nationell multicenter klinisk fas III studie där två olika behandlingsalternativ jämfördes som förstalinjesbehandling vid metastaserad bröstcancer, den sk TEX-studien. Totalt randomiserades 287 patienter mellan cytostatikakombinationerna epirubicin + Taxol (ET) och samma kombination med tillägg av Xeloda (TEX). HRQoL mättes i studie I-III av frågeformuläret EORTC QLQ C-30 som mäter generell livskvalitet. I studie I användes även det

bröstcancerspecifika frågeformuläret EORTC BR-23. Patienterna besvarade frågeformulären vid 5 tidpunkter (innan randomisering, 2 mån, 4 mån, 6 mån och 9 mån efter inklusion). Både kvantitativ (studie I-III) och kvalitativ (studie IV) metod har använts.

Studie I

Syftet med studie I var att jämföra patienternas HRQoL mellan de båda behandlingsarmarna före behandlingsstart och under de första nio månaderna av behandlingen. Totalt besvarade163 patienter besvarade frågeformulären vid alla fem tidpunkterna. Ett speciellt fokus lades på mätpunkterna vid 2 månader, då biverkningarna förväntades vara som värst, och efter 9 månader, då kvinnorna antogs ha anpassat sig till behandlingen. Linjär regressionsanalys användes för att analysera skillnader i hälsorelaterad livskvalitet mellan de båda grupperna, över tid och interaktioner mellan grupp och tid. Vid 9-månadersmätningen fanns en statistisk signifikant skillnad för total livskvalitet och fysisk funktion till fördel för patienter som behandlades med tredrogskombinationen TEX. I övrigt fanns inga skillnader eller interaktioner mellan behandlingsgrupperna och tid.

Studie II

Syftet med studie II var att undersöka om hälsorelaterad livskvalitet kan vara en oberoende prognostisk faktor vid respons på behandling, progressionsfri överlevnad samt total överlevnad.

De 252 patienter som besvarade frågeformulären före randomisering ingick i denna studie. Logistisk regressionsanalys användes och kliniska variabler som kontrollerades för i analysen var ålder, ECOG performance status samt antal metastaslokaler. Fatigue visade ett samband med respons och överlevnad. Det fanns även associationer mellan flera andra HRQoL variabler och respons (rollfunktion, social funktion, illamående och kräkning samt aptitlöshet). Analyserna visade inga samband mellan hälsorelaterad livskvalitet och progressionsfri överlevnad.

Studie III

Syftet med studie III var att undersöka om det fanns samband mellan HRQoL och toxicitet, specifika SNP och toxicitet samt SNP, toxicitet och dess påverkan på livskvalitet. Denna studie baseras på analyser av 28 SNPs från 185 av de 252 patienter som besvarade frågeformulären före randomiseringen. Flera regressionsanalyser har gjorts och vid jämförelse mellan toxicitet och HRQoL visades statistiskt signifikanta samband mellan ett flertal av HRQoL variablerna och

toxicitet (fatigue, värk, andfåddhet, kardiovaskulära besvär, gastrointestinala besvär samt hud besvär). Fatigue och värk var de mest frekventa toxiska reaktionerna. I analysen mellan SNP och toxicitet framkom associationer mellan vissa SNP och toxicitet. Vi fann ett samband mellan specifika SNPs för paclitaxel metabolism och neuropatier, fatigue och hudbesvär samt mellan specifika SNPs som påverkar capecitabine metabolismen och toxicitet såsom slemhinnepåverkan, gastrointestinala besvär och andfåddhet. I de specifika SNPs för epirubicin metabolismen och toxicitet fanns en association till överkänslighetsreaktioner och diarée. Det finns en koppling mellan SNP, toxicitet och livskvalitet.

Studie IV

Studie IV är en kvalitativ intervjustudie med syftet var att studera psykologiska reaktioner hos kvinnor vars sjukdom progredierat efter inklusion i TEX-studien. Totalt inkluderades konsekutivt 20 patienter, två avböjde. Intervjuerna, som ägde rum inom två veckor efter besked om progress, spelades in på band. Kvalitativ innehållsanalys användes vid analys av de utskrivna intervjuerna. Resultatet visade att många av kvinnorna hade känt på sig att de hade progress. Oro var den mest förekommande reaktionen och kvinnorna hade många olika strategier för att hantera situationen och de flesta förstod och accepterade sin situation. Intresse för professionella stödsamtal var litet och många uppgav att de tyckte att deras första recidiv var mer traumatiskt.

Slutsatser från dessa 4 studier är:
- HRQOL över tid ger information som kan användas vid val av behandling, i synnerhet om ingen skillnad i behandlingseffekten mellan valda behandlingsalternativ kan påvisas. Kunskaperna om HRQoL kan också användas vid information till patienterna om vilka effekter på HRQoL de kan förvänta under behandlingen.
- Analyserna visade samband mellan fatigue och respons på behandling samt överlevnad. Mot bakgrund av dessa data bör fatigue hos cancerpatienter identifieras och behandlas. Fatigue kan övervägas som stratifieringsvariabel i framtida kliniska studier i denna population av patienter.

- Analyserna visade ett samband mellan HRQoL och toxicitet, specifika SNP och toxicitet samt samband mellan SNP, toxicitet och dess påverkan på livskvalitet. Dessa kunskaper

kan påverka valet av kemoterapi till denna patientpopulation, beroende på behandlingarnas toxicitetsprofil och dess påverkan på patienternas livskvalitet.

- Patienter som progredierar under behandlingen utvecklar resurser att hantera svåra besked utan uttalade behov av professionellt psykosocialt stöd

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REFERENCES

Aaronson, N.K. (1988).Quality of life: what is it? How should it be measured? *Oncology*, 2(5), 69-76.

Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., Filiberti, A., Fletchtner, H.,et al. (1993). The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*, 85(5), 365-376.

Albain, K.S., Nag, S.M., Calderillo-Ruiz, G., Jordaan, J.P., Llombart, A.C., Pluzanska, A., Rolski, J., Melemed, A.S., et al. (2008). Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *Journal of Clinical Oncology,* 26(24), 3950-3957.

Andersson, M., Lidbrink, E., Bjerre, K., Wist, E., Enevoldsen, K., Jensen, A.B., Karlsson, P., Tange, U.B.,et al. (2011). Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. *Journal of Clinical Oncology*, 29(3), 264-271.

Atalay, G., Biganzoli, L., Renard, F., Paridaens, R., Cufer, T., Coleman, R., Calvert, A. H., Gamucci, T. (2003). Clinical outcome of breast cancer patients with liver metastases alone in the anthracycline-taxane era: a retrospective analysis of two prospective randomized metastatic breast cancer trials. European *Journal of Cancer*, 39(17), 2439-2449.

Bergh, J., Jonsson, P.E., Glimelius, B., Nygren, P. (2001). A systematic overview of chemotherapy effects in breast cancer. *Acta Oncologica*, 40(2-3), 253-281.

Bergman, B., Sullivan, M., Sörenson, S. (1991). Quality of life during chemotherapy for small cell lung cancer. I. An evaluation with generic health measures. *Acta Oncologica*.30 (8):947-957.

Bergman, B., Sullivan, M., Sörenson, S. (1992). Quality of life during chemotherapy for small cell lung cancer. II. A longitudinal study of the EORTC Core Quality of Life Questionnaire and comparison with the Sickness Impact Profile. *Acta Oncologica*.31(1):19-28.

Bergner, M., Bobbitt, R.A., Carter, W.B., Gilson, B.S. (1981). The Sickness Impact Profile: development and final revision of a health status measure. *Medical Care*, 19(8):787-805.

Berry, D.A., Cirrincione, C., Henderson, I.C., Citron, M.L., Budman, D.R., Goldstein, L.J., Martino, S., Perez, E.A. (2006). Estrogen-receptor status and outcomes of modernchemotherapy for patients with node-positive breast cancer. *Journal of the American Medical Association*, 295(14), 1658-1667.

Bjordal, K., de Graff, A., Fayers, P.M., Hammerlid, E., Van Pottelsberghe, C., Curran, D., Ahlner-Elmqvist, M., Maher, E.J., et al. (2000). A 12 Country field of the EORTC QLQ C-30 (version 3.0) and the head and neck specific module (the QLQ-H&N35). *European Journal of Cancer*, 36(14):213-219.

Blackwell, K.L., Burstein, H.J., Storniolo, A.M., Rugo, H., Sledge, G., Koehler, M., Ellis, C., Casey, M., et al. (2010). Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *Journal of Clinical Oncology.*28(7), 1124-30.

Botenbal, M. , Creemers, G.J., Braun, H.J., de Boer, A.C., Janssen, J.T., Leys, R.B., Ruit, J.B., Goey, S.H., et al. (2005). Phase II to III study comparing doxorubicin and dosetaxel with fluorouracil, doxorubicin and cyclophosphamide as first line chemotherapy in patients with metastatic breast cancer:results of Dutch community setting trial for the clinical trial group of the comprehensive cancer centre. *Journal of Clinical Oncology*, 23(28):17081-7088.

Bowling, A. *Measuring disease*. 2nd edition. 2009.

Brooks, R. (1996).EuroQol: the current state of play. *Health Policy*, 37(1):53-72.

Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M., Ramirez, A. (2005). Depression and anxiety in women with early breast cancer: five year observational cohort study. *British medical association*, 330(7493), 1-4.

Cameron, D., Casey, M., Press, M., Lindquist, D., Pienkowski, T., Romieu, C.G., Chan, S., Jagiello-Gruszfeld, A. (2008). Phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Research Treatment,* 112(3):533-543.

Cardoso, F., Bedard, P.L., Winer, E.P., Pagani, O., Senkus-Konefka, E., Fallowfield, L.J., Kyriakides, S., Costa, A., et al. (2009). International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. *Journal of the National Cancer Institute*, 101(17), 1174-1181.

Carmichael, A.R. (2006). Obesity as a risk factor for development and poor prognosis of breast cancer. BJOG: *An International Journal of Obstetrics and gynecology*, 113(10)1160-1166

Carty, N.J., Foggitt, A., Hamilton, C.R., Royle, G.T., Taylor, I., Royle, G.T., Taylor, I. (1995). Patterns of clinical metastasis in breast cancer. An analysis of 100 patients. *European Journal of Surgical Oncology*, 21(6), 607-608.

Cassier, P.A., Chabaud, S., Trillet-Lenoir, V., Peaud, P.Y., Tigaud, J.D., Cure, H., Orfeuvre, H., Salles, B., et al. (2008). A phase III trial of doxorubicin and dosetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: result of the Erasme 3 study. *Breast Cancer Research Treatment*, 109(2):343-350

Cella, D.F & Tulsky, D.S. (1990). Measuring quality of life today: methodological aspects. *Oncology*, 4(5):29-38.

Cella D.F & Tulsky D.S. (1993). Quality of life in cancer: definition, purpose, and method of measurement. *Cancer Investigation*, 11(3), 327-336.

Chang, J., Clark, G., Alfred, D., Mahsin, S., Chamness, G., Elledge, R.M. (2003). Survival of patients with metastatic breast cancer: importance of prognostic markers of the primary tumor. *Cancer.* 97(3).545-553.

Cheung, W.Y., Le, L.W., Zimmermann, C. (2009). Symptom clusters in patients with advanced cancers. *Supportive Care in Cancer*, 17(9), 1223-1230.

Cianfrocca, M & Goldstein, L. (2004). Prognostic and predictive factors in early stage breast cancer. *The Oncologist*, 9(6), 606-616

Clarke, M., Collins, R., Darby, S., Davies, C., Elphinstone, P., Evans,E., Godwin, J., Gray, R., et al. (2005). Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. *Lancet*, 366(9503), 2087-2106.

Coates, A., Dillenbeck, C.F., McNeil, D.R., Kaye, S.B., Sims, K., Fox, R.M., Woods, R.L., Milton, G.W., et al. (1983). On the receiving end--II. Linear analogue self-assessment (LASA) in evaluation of aspects of the quality of life of cancer patients receiving therapy. *European Journal of Cancer & Clinical Oncology*, 19(11):1633-1637.

Coates, A., Keshaviah, A., Thurlimann, B., Mouridsen, H., Mauriac, L., Forbes, J.F., Paridaens, R., Castiglione-Gertsch, M., et al. (2007). Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *Journal of Clinical Oncology*, 25(5), 486–492.

Collaborative Group on Hormonal Factors in Breast Cancer. (1996). Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet*, 347(9017), 1713-1727.

Collaborative Group on Hormonal Factors in Breast Cancer (CGoHFiB). (2001). Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. *The Lancet*, 358(9291), 1389–1399.

Colozza, M., Azambuja, E., Cardoso, F., Sotiriou, C., Larsimont, D., Piccart, M.J.(2005). Proliferative markers as prognostic and predictive tools in early breast cancer: Where are we now? *Annals of Oncology*, 16(11)1723-1739.

Conte, P.F, Guarneri, V., Bruzzi, P., Prochilo, T., Salvadori, B., Bolognesi, A., Aldrighetti, D., Venturini, M., et al. (2004). Concomitant versus Sequential Administration of Epirubicin and Paclitaxel as Fisrt-Line Therapy in Metastatic Breast Cancer. *Cancer*, 101(4)704-712.

Cull, A.M. (1997). Cancer-specific quality of life questionnaires: the state of the art in Europe. *European Journal of Cancer*, 33(Suppl 6):3-7.

Czene, K., Lichtenstein, P., Hemminki, K. (2002). Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. *International Journal of Cancer*,99 (2), 260-266.

Dent, R & Clemons, M. (2006). Trastuzumab after primary treatment for early stage HER2-positive breast cancer reduces recurrence. *Cancer Treatment Reviews*, 32(2):144-148.

Diaz-canton, E.A, Valero, V., Rahman, Z., Rodriguez-Monge, E., Frye, D., Smith, T., Buzdar, A.U., Hortobagyi, G.N. (1998).Clinical course of breast cancer patients with metastases confined to the lungs treated with chemotherapy. The University of Texas M. D Anderson Cancer Center experience and review of the literature. *Annals of Oncology*, 9(4),413-18.

Early Breast Cancer Trialists´ Collaborative Group. (2000).Favourable and unfavourable effects on long-Term survival of radiotherapy for early breast cancer: an overview of the randomized trials. *Lancet*, 355(9217), 1757-1770.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, 20,365(9472), 1687-1717.

Easton, D & Peto, J. (1990). The contribution of inherited predisposition to cancer incidence. *Cancer surveys*, 9(3), 395-416.

Eeles, R.A. (1999).Screening for hereditary cancer and genetic testing, epitomized by breast cancer. *European Journal of Cancer*, 35(14), 1954-1962.

Efficace, F., Biganzoli, L., Piccart, M., Coens, C., Van Steen, K., Cufer, T., Coleman, R.E., Calvert, H.A., et al. (2004). Baseline health-related quality of life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. *European Journal of Cancer*, 40(7)1021-1030.

Elder, E.E., Kennedy, C.W., Gluch, L., Carmalt, H.L., Janu, N.C., Joseph, M.G., Donellan, M.J., Molland, J.G.(2006).Patterns of breast cancer relapse. *European Journal of Surgical Oncology*, 32 (9), 922-927.

Elston, C.W & Ellis, I.O. (1991). Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology*, 19(5), 403-410.

Engholm, G., Ferlay, J., Christensen, N., Bray, F., Gjerstorff, M.L., Klint, Å., Køtlum, J.E., Ólafsdóttir, E. (2010).NORDCAN: Cancer Incidence, Mortality, Prevalence and Prediction in the Nordic Countries, Version 3.7. *Association of the Nordic Cancer Registries*. Danish Cancer Society (http://www.ancr.nu).

Er, O., Frye, D.K., Kau, S.W., Broglio, K., Valero, V., Hortobagyi, G.N., Arun, B. (2008). Clinical course of breast cancer patients with metastases limited to the liver treated with chemotherapy. *Cancer Journal*, 14(1), 62-68.

Esserman, L & Shieh, A.B. (2009).Thompson I. Rethinking Screening for Breast Cancer and Prostate Cancer. *Journal of the American Medical Association*, 302(15):1685-92.

Fagerholm, R., Hofstetter, B., Tommiska, J., Aaltonen, K., Vrtel, R., Syrjäkoski, K., Kallioniemi, A., Kilpivaara, O., et al .(2008) NAD(P)H:quinone oxidoreductase 1 NQO1*2 genotype (P187S) is a strong prognostic and predictive factor in breast cancer. *Nature Genetics*, 40(7), 844–853.

Fasching, P.A, Kollmannsberger, B., Strissel, P.L., Niesler, B., Engel, J., Kreis, H., Lux, M.P., Weihbrecht, S., et al. (2008). Polymorphisms in the novel serotonin receptor subunit gene HTR3C show different risks for acute chemotherapy-induced vomiting after anthracycline chemotherapy. *Journal of Cancer Research and Clinical Oncology*, 134(10), 1079-1086

Fayers, P.M., Aaronson, N.K., Bjordal, K., Groenvold, M., et al (2001) *On behalf of the EORTC quality of life group EORTC QLQ-C30 scoring manual, 3rd edn*. EORTC, Brussels

Fayers, P., Bottomley, A.; EORTC Quality of Life Group; Quality of Life Unit. (2002). Quality of life research within the EORTC-the EORTC QLQ-C30. *European Organisation for Research and Treatment of Cancer. European Journal of Cancer.*38, (Suppl 4),125-133.

Fayers, P & Machin, D. (2009). *Quality of Life. The assessment, analysis and interpretation of patient-reported outcomes*. 2nd edition.

Fisher, B., Anderson, S., Redmond, C.K., Wolmark, N., Wickerham, D.L., Cronin, W.M.(1995). Reanalysis and results after 12 years of follow-up in a randomized clinical trial Comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *New England Journal of Medicine*, 333(22)1456-1461.

Fisher, B., Anderson, S., Bryant, J., Margolese, R.G., Deutsch, M., Fisher, E.R., Jeong, J.H, Wolmark, N. (2002). Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomyplus irradiation for the treatment of invasive breast cancer. *New England Journal of Medicine*, 347(16), 1233–1241.

Fossati, R., Confalonieri, C., Torri, V., Ghislandi, E., Penna, A., Pistotti, V., Tinazzi, A., Liberati, A. (1998).Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomised trials involving 31,510 women. *Journal of Clinical Oncoogy*, 16 (10), 3439 – 3460.

Frazer, K.A., Ballinger, D.G., Cox, D.R., Hinds, D.A., Stuve, L.L., Gibbs, R.A., Belmont, J.W., Boudreau, A., et al. International HapMap Consortium (2007). A second generation human haplotype map of over 3.1 million SNPs. *Nature*, 449(7164), 851-861.

Garatt, A., Schmidt, L., Mackintosh, A., Fitzpatrick, R. (2002). Quality of life measurement: bibliographic study of patient assessed health outcome measures. *British Medical Journal*, 324(7351)1417-1419.

Gerber, B., Freund, M., Reimer, T. (2010). Recurrent breast cancer: treatment strategies for maintaining and prolonging good quality of life. *Deutsches Ärzteblatt international*, 107(6):85-91.

Ghersi, D., Wilcken, N., Simes, R.J. (2003). A systematic review of taxane-containing regimens for metastatic breast cancer. *British Journal of Cancer*, 93(3), 293-301

Gianni, L., Dafni, U., Gelber, R.D., Azambuja, E., Muehlbauer, S., Goldhirsch, A., Untch, M., Smith, I. (2011). Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncology*, 12(3)236–244.

Gill, T.M & Einstein, A.R. (1994). A critical appraisal of quality-of-life measurements. *Journal of the American Medical Association*, 272(8), 619-626.

Goldhirsch, A., Wood, W.C., Gelber, R.D., Coates, A.S., Thürlimann, B., Senn, H.J; 10th St. Gallen conference. (2007). Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Annals of Oncology*, 18(7)1133-1144.

Gomez, H.L., Doval, D.C., Chavez, M.A., Ang, P.C., Aziz, Z., Nag, S., Ng, C., Franco, S.X., et al. (2008. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. *Journal of Clinical Oncology*, 26(18):2999-3005

Graneheim, U. H., & Lundman, B. (2004). Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Education Today*, 24(2), 105-112.

Groenvold, M., Petersen, M.A., Idler, E., Bjorner, J.B., Fayers, P.M., Mouridsen, H.T. (2007). Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. *Breast Cancer Research Treatment*, 105(2), 209-219.

Hackbarth, M., Haas, N., Fotopoulou, C., Lichtenegger, W., Sehouli, J. (2008) Chemotherapy-induced dermatological toxicity: frequencis and impact on quality of life in women´s cancers. Results of a prospective study. *Supportive Care of Cancer*, 16(3):267-273.

Harris, L., Fritsche, H., Mennel, R., Norton, L., Ravdin, P., Taube, S., Somerfield, M.R., Hayes, D.F. (2007). American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *Journal of Clinical Oncology*, 25(33), 5287-5312.

Hatoum, H.T., Lin, S.J., Smith, M.R., Barghout, V., Lipton, A. (2008). Zoledronic acid and skeletal complications in patients with solid tumors and bone metastases: analysis of a national medical claims database .*Cancer*, 113(6):1438-1445.

Hayat, M.J., Howlaser, N., Reichman, M.E., Edwards, B.K. (2007). Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and end results (SEER) Program. *Oncologist*, 12(1), 20-37.

Henderson, I.C., Berry, D.A., Demetri, G.D., Cirrincione, C.T., Goldstein, L.J., Martino, S., Ingle, J.N., Cooper, M.R. (2003). Improved outcomes from adding sequential paclitaxelbut not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *Journal of Clinical Oncology*, 21(6), 976-983.

Hermansen, C., Skovgaard Poulsen, H., Jensen, J., Langfeldt, B., Steenskov, V., Frederiksen, P., Jensen, O.M. (1987). Diagnostic reliability of combined physical examination, mammography and fine-needle puncture (triple-test) in breast tumors. A prospective study. *Cancer*, 60(6), 1866-1871.

 Heyes, G.J., Mill, A.J., Charles, M.W. (2009). Mammography-oncogenecity at low doses. *Journal of radiological protection*, 29 (2A): A123 – 132.

Hokken, J.W.E., Van der Cruijsen-raaijmakers, M., Schep, G., Vreugdenhil, G. (2009). Impact of anthracycline dose on quality of life and rehabilitation in breast cancer treatment. *The Netherlands Journal of Medicine*, 67(6), 220-225.

Hunt, S.M., McKenna, S.P., McEwen, J., Williams, J., Papp, E. (1981) The Nottingham Health Profile: subjective health status and medical consultations. *Social science & medicine*, 15(3):221-229.

Jassem, J., Pienkowski, T., Pluzanska, A., Jelic, S., Gorbunova, V., Mrsic-Krmpotic, Z., Berzins, J., Nagykalnai, T., et al. (2001). Doxorubicin and paclitaxel versus fluorouracil, doxorubicin and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. *Journal of Clinical Oncology*, 19(6), 1707-1715

Jenkinson, C., Stewart-Brown, S., Paterson, S., Paice, C. (1999). Assessment of the SF-36 version 2 in the United Kingdom. *Journal of Epidemiology and Community Health*, 53(1), 46-50

Joensuu, H., Kellokumpu-Lehtinen, P.L., Bono, P., Alanko, T., Kataja, V., Asola, R., Utriainen, T., Kokko, R. (2006). Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *New England Journal of Medicine*, 354(8), 809-820.

Johnson, M.R., Hageboutros, A.,Wang, K., High, L., Smith, J.B., Diasio, R.B. (1999) Life-threatening toxicity in a dihydropyrimidine dehydrogenase-deficient patient after treatment with topical 5-fluorouracil. *Clinical Cancer Research*, 5(8):2006-2011.

Jones, S., Holmes, F.A., O'Shaughnessy, J., Blum, J.L., Vukelja, S.J., McIntyre, K.J., Pippen, J.E., Bordelon, J.H. (2009). Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. *Journal of Clinical Oncology*, 27(8), 1177-1183.

Kaasa, S., Brenne, E., Lund, J.A., Fayers, P., Falkmer, U., Holmberg, M., Lagerlund, M., Bruland, O. (2006). Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy x 1) versus multiple fractions (3 Gy x 10) in the treatment of painful bone metastases. *Radiotherapy and Oncology*, 79(3), 278-284.

Kamby, C., Vejborg, I., Daugaard, S., Guldhammer, B., Dirksen, H., Rossing, N., Mouridsen, H.T. (1987). Clinical and radiological characteristics of bone metastases in breast cancer. *Cancer*, 60(10), 2524–2531.

Kamby, C. (1990). The pattern of metastases in human breast cancer: methodological aspects and influence of prognostic factors. *Cancer Treatment Reviews*, 17(1), 37–61.

Kerlikowske, K., Grady, D., Rubin, S.M., Sandrock, C., Ernster, V.L. (1995). Efficacy of screening mammography. A meta-analysis. Journal *of the American Medical Association*, 273(2):149-54.

Key, T., Verasalo, P., Banks, E. (2001). Epidemiology of breast cancer. *Lancet Oncology*, 2(3), 133-140.

Kim, S.H., Son, B.H., Hwang, S.Y., Han, W., Yang, J.H., Lee, S., Yun, Y.H. (2008). Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates and association with quality of life. *Journal of pain and symptom management*, 35(6), 644-655.

Kissane, D.W., Grabsch, B., Clarke, D.M., Smith, G.C., Love, A.W., Bloch, S., Snyder, R.D., Li, Y. (2007). Supportive-expressive group therapy for womenwith metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial. *Psychooncology*, 16(4), 277-286.

Krag, D., Weaver, D., Ashikaga, T., Moffat, F., Klimberg, V.S., Shriver, C., Feldman, S., Kusminsky, R., et al. (1998)The sentinel node in breast cancer – a multicenter validation study. *New England Journal of Medicine*, 339(14), 941-946.

Kramer, J.A., Curran, D., Piccart, M., de Haes, J.C., Bruning, P., Klijn, J., Van Hoorebeeck, I., Paridaens, R. (2000).Identification and interpretation of clinical and quality of life prognostic

factors for survival and response to treatment in first-line chemotherapy in advanced breast cancer. *European Journal of Cancer*, 36(12), 1498-1506.

Krippendorff, K. *Content analysis: an introduction to its methodology*. 2nd ed. Thousand Oaks, Calif.: Sage; 2004.

Lamba, J.K., Crews, K., Pounds, S., Schuetz, E.G., Gresham, J., Gandhi, V., Plunkett, W., Rubnitz, J., et al. (2007). Pharmacogenetics of deoxycytidine kinase: identification and characterization of novel genetic variants. *The Journal of pharmacology and experimental therapeutics*, 323(3): 935–945.

Largillier, R., Ferrero, J.M., Doyen, J., Barriere, J., Namer, M., Mari, V., Courdi, A., Hannoun-Levi, J.M., et al. (2008). Prognostic factors in 1038 women with metastatic breast cancer. *Annals of Oncology*, 19(12), 2012-2019.

Lehman, A.F., Rachuba, L.T., Postrado, L.T. (1995). Demographic influences on quality of life among persons with chronic mental illness. *Evaluation and Program Planning*, 18:155-164.

Li, Y., Baer, D., Friedman, G,D., Udaltsova, N., Shim, V., Klatsky, A.L. (2009). Wine, Liquor, beer and risk of breast cancer in a large population. *European Journal of Cancer*, 45(5),843-850.

Liu, M.T., Huang, W.T., Wang, A.Y., Huang, C.C., Huang, C.Y., Chang, T.H., Pi, C.P., Yang, H.H. (2010). Prediction of outcome of patients with metastatic breast cancer: evaluation with prognostic factors and Nottingham prognostic index. *Supportive care in cancer*, 18(12),1553-1564.

Lostumbo, L., Carbine, N.E., Wallace, J. (2010).Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database System Review*. 11:CD002748.

Mamounas, E.P., Bryant, J., Lembersky, B., Fehrenbacher, L., Sedlacek, S.M., Fisher, B., Wickerham, D.L., Yothers, G. (2005).Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. *Journal of Clinical Oncology*, 23(16)3686-3696.

Martin, M., Liuch, A., Segúl, M.A., Ruiz, A., Ramos, M., Adrover, E., Rodríguez-Lescure, A., Grosse, R., et al.(2006).Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) : impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. *Annals of Oncology*, 17(8), 1205-1212.

Marty, M., Coggnetti, F., Maraninchi, D., Snyder, R., Mauriac, L., Tubiana-Hulin, M., Chan, S., Grimes, D., et al. (2005). Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administred as first-line treatment: the M77001 Study Group. *Journal of Clinical Oncology*, 23(19)4265-4274.

Mauri, D., Kamposioras, K., Tsali, L., Bristianou, M., Valachis, A., Karathanasi, I., Georgiou, C., Polyzos, N.P. (2010). Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: A meta-analysis. *Cancer Treatment Review*, 36(1):69-74.

Michelsson, H., Bolund, C., Nilssson, B., Brandberg, Y. (2000). Health-related Quality of Life Measured by the EORTC QLQ-C30- reference values from a large sample of the Swedish population. *Acta Oncoloiga*, 39(4), 477-484.

Mieog, J.S.D., van der Hage, J.A., van de Velde, C.J.H. (2007). Postoperative chemotherapy for women with operable breast cancer. *The Cochrane Database of Systematic Reviews*, 18(2).

Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P.A., Harshman, K., Tavtigian, S., Liu, Q., Cochran, C., et al.(1994).A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science*, 266(5182), 66-71.

Nabholtz, J.M , Senn, H.J., Bezwoda, W.R., Melnychuk, D., Deschênes, L., Douma, J., Vandenberg, T.A., Rapoport, B., et al .(1999). Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy.304 Study Group. *Journal of Clinical Oncology* .17 (5), 1413 – 1424.

Nabboltz, J.M., Falkson, C., Campos, D., Szanto, J., Martin, M., Chan, S., Pienkowski, T., Zaluski, J. et al., (2003). Dosetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of randomized, multicenter, phase III trial. *Journal of Clinical Oncology*, 21(6), 968-975.

Nabbholtz, J.M. (2008). Long-term safety of aromatase inhibitors in the treatment of breast cancer. *Therapeutics and Clinical risk management*, 4(1), 189-204.

National Cancer Institute (1999) *Common Toxicity Criteria, version 2.0.* http://ctep.cancer.gov/reporting/ctc.html.

Nistico, C., Cuppone, F., Bria, E., Fornier, M., Giannarelli, D., Mottolese, M., Novelli, F., Natoli, G., et al. (2006). Ten years of experience with weekly chemotherapy in metastatic breast cancer patients: multivariate analysis of prognostic factors. *Anticancer Drugs*. 2006; 17(10), 1193-1200.

Nystrom, L., Andersson, I., Bjurstam, N., Frisell, J., Nordenskjöld B,., Rutqvist, L.E. (2002). Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet*, 359(9310):909-919

O'Shaughnessy, J., Miles, D., Vukelja, S., Moiseyenko, V., Ayoub, J.P., Cervantes, G., Fumoleau, P., Jones S., et al. (2002). Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *Journal of Clinical Oncology*, 20(12)2812-2823.

O'Shaughnessy, J. (2005). Extending survival with chemotherapy in metastatic breast cancer. *Oncologist*, 10(suppl 3), 20-29.

Osoba, D., Aaronson, N.K., Zee, B., Sprangers, M.A.G., te Velde, A. (1997).Modification of the EORTC QLQC30 (version 2.0) based upon content validity and reliability testing in large samples of patients with cancer. *Quality of Life Research*, 6(2)103-108.

Osoba, D., Rodrigues, G., Myles, J., Zee, B., Pater, J. (1998). Interpreting the significance of changes in health-related quality-of-life scores. *Journal of Clinical Oncology*, 16(1):139-144.

Owens, M.A., Horten, B.C., Da Silva, M.M. (2004). HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. *Clinical Breast Cancer*, 5(1), 63–69.

Pavlakis, N., Schmidt, R., Stockler, M. (2005). Bisphosphonates for breast cancer. *The Cochrane database of systematic reviews*,20,(3).

Peplonska, B., Lissowska, J., Hartman, T.J., Szeszenia-Dabrowska, N., Blair, A., Zatonski, W., Sherman, M.E., Garcia-Closas, M., et al. (2008). Adulthood lifetime physical activity and breast cancer. *Epidemiology*, 19(2), 226-236.

Pharoah, P.D.P., Day, N.E., Duffy, S., Easton, D., Ponder, B.A. (1997). Family history and risk of breast cancer: a systematic review and meta-analysis. *International Journal of Cancer*, 71(5), 800-809.

Piccart-Gebhart, M.J., Procter, M., Leyland-Jones, B., Goldhirsch, A., Untch, M., Smith, I., Gianni, L. (2005). Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine*, 353(16), 1659-1672.

Porch, J.V., Lee, I.M., Cook, N.R., Rexrode, K.M., Burin, J.E. (2002). Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). *Cancer Causes Control*, 13(9):847-854.

Quinten, C., Coens, C., Mauer, M., Comte, S., Sprangers, M.A., Cleeland, C., Osoba, D., Bjordal, K., Bottomley, A.; EORTC Clinical Groups. (2009). Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. *Lancet Oncology*, 10(9), 865-871.

Rebbeck, T.R., Fribel, T., Lynch, H.T., Neuhausen, S.L., van 't Veer, L., Garber, J.E., Evans, G.R., Narod, S.A., et al. (2004).Bilateral Prophylatic Mastectomy Reduces Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: The Prose Study Group. *Journal of Clinical Oncology*, 22(6)1055-1062

Reese, D.M., Slamon, D.J. (1997). HER-2/neu signal transduction in human breast and ovarian cancer. *Stem Cells*, 15(1), 1–8.

Ribelles, N., Lopez-Siles, J., Sanchez, A., González, E., Sánchez, M.J., Carabantes, F., Sánchez-Rovira, P., Márquez, A., et al. (2008) A carboxylesterase 2 genepolymorphismas predictor of capecitabine on response and time to progression. *Current Drug Metabolism*, 9(4):336–343.

Ryberg, M., Nielsen, D., Cortese, G., Nielsen, G., Skovsgaard, T., Andersen, P.K. (2008) New insight into epirubicin cardiac toxicity: competing risks analysis of 1097 breast cancer patients. *Journal of the National Cancer Institute*, 100(15), 1058-1067.

Saphner T., Tormey D.C., Gray R. (1996). Annual hazard rates of recurrence for breast cancer after primary therapy. *Journal of Clinical Oncology*, 14(10), 2738–2746.

Schwartz, C.E., Sprangers, M.A.(2002). An Introduction to Quality of Life Assessment in Oncology: The Value of Measuring Patient-Reported Outcomes. *The American Journal of Managed Care*, 8(18 suppl), 550-559.

Schwartzberg, Lee S., Cobb, P., Walker, M.S., Stepanski, E., Houts, A.C. (2009). Patient and practice impact of capecitabine compared to taxanes in first-/second-line chemotherapy for metastatic breast cancer. *Supportive Care in Cancer*, 17(8), 1081-1088.

Seidman, A.D, O´Shaughnessy, J., Misset, J.L. (2002) Single-agent capecitabine: a reference treatment for taxane-pretreatment metastatic breast cancer? *Oncologist*, 7(Suppl 6), 20-28.

Sherry, M.M., Greco, F.A., Johnson, D.A., Hainsworth, J.D. (1986).Metastatic breast cancer confined to the skeletal system: an indolentdisease. *American Journal of Medicine*, 81(3)381–386.

Sigurdardóttir, V., Bolund, C., Brandberg, Y., Sullivan, M. (1993).The impact of generalized malignant melanoma on quality of life evaluated by the EORTC questionnaire technique. *Quality of life research*, 2(3), 193-203.

Sigurdardóttir, V., Bolund, C., Sullivan, M. (1996).Quality of life evaluation by the EORTC questionnaire technique in patients with generalized malignant melanoma on chemotherapy. *Acta Oncologica*, 35(2), 149-158.

Sissung, T.M. , Mross, K., Steinberg, S.M., Behringer, D., Figg, W.D., Sparreboom, A., Mielke, S. (2006). Association of ABCB1 genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia. *European Journal of Cancer*, 42(17):,2893-2896.

Slamon, D.J., Clark, G.M., Wong, S.G., Levin, W.J., Ullrich, A., McGuire, W.L. (1987).Human breast cancer:correlation of relapse and survival with amplifi cation of the HER-2/neu oncogene. *Science*, 235(4785), 177–182.

Slamon, D.J., Godolphin, W., Jones, L.A., Holt, J.A., Wong, S.G., Keith, D.E., Levin, W.J., Stuart, S.G., et al. (1989). Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*, 244(4905), 707–712.

Slamon, D., Leyland-Jones, B., Shak, S., Fuchs, H., Paton,V., Bajamonde, A., Fleming, T., Eiermann, W., et.al. (2001). Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *New England Journal of Medicine*, 344(11), 783-792.

Smith, I., Procter, M., Gelber, R.D., Guillaume, S., Feyereislova, A., Dowsett, M., Goldhirsch, A., Untch, M. (2007). 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*, 369(9555), 29-36.

Socialstyrelsen. *Cancer incidens in Sweden 2009*. (2010) Stockholm. The National Board of Health and Welfare. http://www.socialstyrelsen.se/publikationer2010/).

Solomayer, E.F., Diel, I.J., Meyberg, G.C., Gollan, C., Bastert, G. (2000). Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Research Treatment*, 59(3), 271–278.

Sparano, J.A , Wang, M. , Martino, S. , Jones, V., Perez, E.A., Saphner, T., Wolff, A.C., Sledge, G.W. Jr., et al .(2008). Weekly paclitaxel in the adjuvanttreatment of breast cancer. *New England Journal of Medicine*, 358 (16), 1663-1671.

Sprangers, M.A., Cull, A., Bjordal, K., Groenvold, M., Aaronson, N.K. (1993).The European Organisation for Research and Treatment of Cancer approach to quality of life assessment: guidelines for developing questionnaire modules. *Quality of Life Research*, 2(4), 287-295.

Sprangers, M.A., Groenvold, M., Arraras, J.I., Franklin, J., te Velde, A., Muller, M., Franzini, L., Williams, A., et al. (1996). The EORTC breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *Journal of Clinical Oncology*, 14(10), 2756-2768.

Sullivan, M. & Karlsson, J. (1998). The Swedish SF-36 Health Survey III. Evaluation of Criterion-Based Validity: Results from Normative population. *Journal of Clinical Epidemiology*, 51(11), 1105-1113.

Tan, S.H., Lee, S.C., Goh, B.C., Wong, J. (2008). Pharmacogenetics in breast cancer therapy. *Clinical Cancer Research*, 14(24), 8027-8041.

Therasse, P., Arbuck, S.G., Eisenhauer, E.A., Wanders, J., Kaplan, R.S., Rubinstein, L., Verweij, J., Van Glabbeke, M. (2000). New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute*, 92(3), 205-216.

Turner, J., Kelly, B., Swanson, C., Allison, R., Wetzig, N. (2005). Psychosocial impact of newly diagnosed advanced breast cancer. *Psychooncology*, 14(5), 396-407.

Veronesi, U., Salvadori, B., Luini, A., Greco, M., Saccozzi, R., del Vecchio, M., Mariani, L., Zurrida, S., Rilke, F. (1995). Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomized trials on 1,973 patients. *European Journal of Cancer*, 31A (10), 1574-1579.

Veronesi, U., Cascinelli, N., Mariani, L., Greco, M., Saccozzi, R., Luini, A., Aguilar, M., Marubini, E. (2002).Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *New England Journal of Medicine*.17; 347(16), 1227-1232.

Veronesi, U., Boyle, P., Goldhirsch, A., Orecchia, R., Viale, G. Breast Cancer. (2005). *Discovery Medicine*, 5(27), 271-277.

Vetto, J., Pommier, R., Schmidt, W., Wachtel, M., DuBois, P., Jones, M., Thurmond, A . (1995). Use of the "triple test" for palpable breast lesions yields high diagnostic accuracy and cost savings.*American Journal of Surgery*, 169(5), 519-522.

Ware, J. E., Snow, K. K., Kosinski, M., & Gandek, B. (1993).
SF-36 Health Survey: Manual and interpretation guide. Boston: Nimrod Press.

WHO. *Constitution of the world Health Organization*. International Health Conference; 1946; New York; 1946.

WHO *Handbook for Reporting Results of Cancer Treatment*. WHO Offset Publication no. 48, World Health Organization, Geneva, 1979.

WHOQOL Group. The *World Health Organization quality of Life assessment* (WHOQOL). WHO (1993b). WHOQOL Study Protocol. WHO(MNH/PSF/939.

Winer, E.P., Berry, D.A., Woolf, S., Duggan, D., Kornblith, A., Harris, L.N., Michaelson, R.A., Kirshner, J.A., et al. (2004). Failure of higher dose paclitaxel to improve outcome in patients with metastatic breast cancer: Cancer and leukemia group B trial 9342. *Journal of Clinical Oncology*, 22(11):2061-2068.

Welt, A., von Minckwitz, G., Oberhoff, C., Borquez, D., Schleucher, R., Loibl, S., Harstrick, A., Kaufmann, M., et al. (2005). Phase I/II study of capecitabine and vinorelbine in pretreated patients with metastatic breast cancer. *Annals of Oncology*, 16(1), 64-69.

WMA. (2008). *World Medical Association Declaration of Helsinki*.
http://www.wma.net/en/20activities/10ethics/index.html.

Wolff, A.C., Hammond, M.E., Schwartz, J.N., Hagerty, K.L., Allred, D.C., Cote, R.J., Dowsett, M., Fitzgibbons, P.L., et al. (Antonio). American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *Archives of Pathology & Laboratory Medicine*, 131(1)18-43.

Wooster, R., Bignell, G., Lancaster, J., Swift, S., Seal, S., Mangion, J., Collins, N., Gregory, S., et al. (1995). Identification of the breast cancer susceptibility gene BRCA2. *Nature* 378(6559)789-792.

Zinger, JW, Hortobagyi, GN, Buzdar, AU, Smith, T.L, Frashini, G. (1987). Clinical course of breast cancer patients with liver metastases. *Journal of Clinical Oncology*, 5(5)773-782.