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THE EFFECTS OF BREAST CANCER TREATMENT ON COGNITIVE FUNCTIONS

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ABSTRACT

Aims Women with breast cancer have reported difficulties with memory, attention, and concentration during or after adjuvant treatment. Whether these symptoms are side effects of treatment has not been established. The aim of this project was to determine the effects of early-stage breast cancer (BC) diagnosis and treatment on cognitive functions, quality of life, and psychological wellbeing. A secondary aim was to identify any associations between cognitive, psychosocial, somatic, and treatment factors and time to return to work (RTW) among women treated for early-stage BC.

Methods From the mammography screening program at Stockholm South General Hospital, we prospectively enrolled women aged 40 to 69 years who had a positive radiographic finding. All women completed the Headminder Web-based neuropsychological battery Cognitive Stability Index for response speed, processing speed, memory, and attention before diagnosis (T1), after surgery but before adjuvant treatment (T2), 6 months after starting adjuvant treatment (T3), and after another 3 months of follow-up (T4). Women with BC were divided into those receiving chemotherapy, hormone therapy, or no adjuvant medical therapy. Women eventually determined not to have BC served as healthy controls. At each test session, depression, anxiety, and quality of life were measured using the Swedish version of the Beck Depression Inventory, the Beck Anxiety Inventory, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and its BC supplementary measure. The secondary aim was addressed by comparing the above-mentioned scores from BC women who had returned to work with those who had not, at both T3 and T4. We also reviewed the medical certificates of women still on sick leave at 8, 11, and 18 months after diagnosis to determine why they had not returned to work.

Results and Conclusion Of the 146 women enrolled, 77 had BC, of whom 18 received chemotherapy; 45, hormone therapy, and 14, no adjuvant medical therapy; 69 were healthy controls. At baseline, only response speed and processing speed differed significantly between groups. Our results suggest that a diagnosis of BC and subsequent surgery are not associated with substantial cognitive decline. However, the lack of improvement in attention at retest among BC patients may suggest a decline. Further, our results indicate subtle cognitive changes related to time and treatment. Chemotherapy may impair memory and response speed in women with BC, a finding consistent with those reported for BC survivors after adjuvant medical treatment. Breast cancer surgery and adjuvant treatment, irrespectively of type, reduces quality of life and psychological wellbeing, mostly related to time course. Global quality of life health status improved to baseline after 11 months from diagnosis. However, poor body image and lower subjective cognitive functions were sustained and should be addressed in long-term survivors of breast cancer to improve overall quality of life. Chemotherapy is associated with longer periods of sick leave. Cognitive functioning, objectively measured, does not predict RTW. Independently of any adjuvant therapy, most women eventually return to work in a few months. The ability to predict RTW after BC treatment should help prepare higher-risk women for delayed RTW and allow earlier interventions to restore their social relations and quality of life.

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LIST OF PUBLICATIONS

I **The Effects of Breast Cancer Diagnosis and Surgery on Cognitive Functions.**
Hedayati E, Schedin A, Nyman H, Alinaghizadeh H, Albertsson M.
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II **Effects of Adjuvant Treatment on Cognitive Function in Women with Early Breast Cancer.**
Hedayati E, Alinaghizadeh H, Schedin A, Nyman H, Albertsson M.
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III **Quality of Life in Women Before and After Breast Cancer Diagnosis and Treatment.**
Hedayati E, Alinaghizadeh H, Schedin A, Nyman H, Albertsson M.
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IV **Cognitive, Psychosocial, Somatic, and Treatment Factors Predicting Return to Work after Breast Cancer Treatment.**
Hedayati E, Johnsson A, Alinaghizadeh H, Schedin A, Nyman H, Albertsson M
Submitted to Scand J Caring Sci, under revision for resubmission.

CONTENTS

LIST OF ABBREVIATIONS

HER-2 receptor	Human Epidermal Growth Factor Receptor 2
SERM	Selective Estrogen Receptor Modulator
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
EEG	Electroencephalogram
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor alpha
RTW	Return to work
BDI-II	Beck Depression Inventory, Second Edition
BAI	Beck Anxiety Inventory
EORTC QLQ C-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
QLQ BR-23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module

Table 1. A summary of the main features of methods used in the four studies in this project

Study	Title	Study sample	Study design	Outcome	Statistical methods	Measure	Model	Groups
Study I Acta Oncol. 2011	The Effects of Breast Cancer Diagnosis and Surgery on Cognitive Functions	Swedish women 40-69 years, re-assessed for BC as a result of a positive radiographic finding	Longitudinal	Memory, Attention, Processing speed, Response speed	Mixed model	LSMEAN	Model I, II & III	BC, HC
Study II Eur J Oncol Nurs. 2011	Effects of Adjuvant Treatment on Cognitive Function in Women with Early Breast Cancer	Swedish women 40-69 years, with early BC treated with surgery and adjuvant therapy.	Longitudinal	Memory, Attention, Processing speed, Response speed	Mixed model	LSMEAN	Model IV, V & VI	BC consisting of three treatment groups: chemotherapy, hormone therapy, no adjuvant medical therapy; HC
Study III Eur J Oncol Nurs. (Submitted 2011)	Quality of Life in Women Before and After Breast Cancer Diagnosis and Treatment	Swedish women 40-69 years, with early BC treated with surgery and adjuvant therapy.	Longitudinal	Quality of life, Depression, Anxiety	Mixed model	LSMEAN	Model I	BC consisting of three sub-groups: chemotherapy, hormone therapy, no adjuvant medical therapy; HC
Study IV Scand J Caring Sci. (Resubmitted 2011)	Cognitive, Psychosocial, Somatic, and Treatment Factors Predicting Return to Work after Breast Cancer Treatment	Swedish women with BC 40-64 years, who reported having worked part-time or full-time before their original diagnosis	Longitudinal	Return to work	Generalized linear model	OR	Model I & VII	Working, Sick-leave

Measures; LSMEAN= least-squares-means, OR=odds ratio. **Models:** Model I= unadjusted. Model II= Adjusted for age. Model IIi=Adjusted for age, education level, pain, B-hemoglobin, depression, and anxiety. Model IV= Adjusted for age and education level. Model V=Adjusted for hemoglobin count, depression, anxiety, pain, and fatigue. Model VI= Adjusted for baseline domain scores, educational level, and age tertiles. Model VII= Adjusted for age, education, marital status, and work status. **Groups**: BC= Breast Cancer, HC= Healthy Controls.

1 INTRODUCTION

Breast cancer is the most common malignancy affecting women in Sweden, accounting for about 30% of cancer cases in women annually [1]. Breast cancer incidence increases with age, and survival rates have continuously improved [1] as a result of better systemic early detection through screening, effective diagnostic pathways, and more effective local and systemic treatment. Thus, the number of women who survive this cancer is rising, which has increased interest in the longer-term effects of treatment, such as general functioning, quality of life, and return to work.

Today, cancer treatments are complex and include surgery, chemotherapy, endocrine treatment, and targeted therapies. These treatments reduce health-related quality of life, and women receiving adjuvant therapy often report difficulties with memory, attention, and concentration [2,3].

The effect of breast cancer and its treatment on cognitive functions remains an important area of research; therefore we conducted a longitudinal, prospective study to investigate the cognitive functions in women who had been screened for breast cancer, before breast cancer was diagnosed, after surgery, and after adjuvant treatment.

We sought to determine whether measures of cognitive function changed over time in women with early breast cancer treated with surgery and adjuvant chemotherapy, adjuvant hormone therapy, or no adjuvant medical therapy and whether these measures differed from those of healthy women. We assessed cognitive function before cancer was diagnosed and therefore before primary and adjuvant treatment. Our design is unique in that our control group consisted of healthy women without breast cancer but who had undergone the same stresses of diagnostic re-assessment.

1.1 BREAST CANCER DIAGNOSIS AND TREATMENT

The Swedish Two-Country Trial of mammographic screening was the first breast screening trial to show a 30% reduction in breast cancer mortality from screening with mammography alone, among 40-to-74-year-old women invited to screening [4]. The County of Stockholm's decision to screen all women aged between 40 and 50 years was made coincidentally at the start of our study, leading to more re-assessment of healthy women in this age group. The mammography screening program at the Mammography Department of Stockholm South General Hospital serves healthy women living in Stockholm County aged 40 to 69 years. The program examined about 800 women weekly in 2006. About 20 (2.5%) of these women are recalled each week

for further assessment as a result of positive mammographic findings, and 10 of these are examined by an oncologist or a breast surgeon, 5 of whom are eventually diagnosed with breast cancer. The other 10 women, in whom further mammograms from several angles revealed no evidence of breast cancer, continue with the standard mammography screening program.

If a suspicious "spot" is identified on a screening mammogram, the woman is asked to return for further assessment with complementary radiographic views. The radiologist then decides whether the radiograph is benign, probably benign, or remains suspicious for cancer. Women with benign findings are asked to return at the next scheduled routine screening exam, 18 to 24 months later. Women with findings that are probably benign or suspicious for cancer are referred to an oncologist or a breast surgeon for further examination and to undergo fine-needle aspiration cytology or biopsy.

Breast surgery is considered primary treatment for early breast cancer. Complete surgical resection has been a critical part of management since the late 1800s [5]. The aims of surgery are to completely resect the primary tumor to reduce the risk of local recurrences and to stage the tumor and axillary lymph nodes to obtain prognostic information. Breast conservation surgery (sector resection) is now the standard of care for women with early-stage breast cancer. Notwithstanding, mastectomy is indicated for some women on the basis of tumor size or location, multifocality, or inflammation and may be chosen by the patient. At least two-thirds of women are eligible for breast conservation surgery, but rates of mastectomy vary both geographically and institutionally [6]. Radiotherapy is important after breast-conserving surgery because it can reduce the incidence of local recurrence and may improve overall survival in specific settings [7].

In early-stage breast cancer, potentially viable tumor cells can be disseminated; the role of systemic adjuvant therapy is to destroy these cells [8]. Adjuvant systemic therapy refers to chemotherapy, hormonal therapy, and targeted biological agents administered after the primary tumor is resected. Incorporating adjuvant systemic therapies into the multidisciplinary management of breast cancer has improved disease-free and overall survival rates [6]. Indications for adjuvant systemic therapy after surgery are established prognostic factors, including age, menopausal status, co-morbidities, axillary-lymph-node involvement, tumor size, tumor grade, and intrinsic biological features of the tumor, including proliferation rate, hormone receptor status, and expression of human epidermal growth factor receptor 2 (HER-2) [9,10].

1.2 OVERVIEW OF COGNITIVE FUNCTIONING

Cognitive functions commonly include a variety of skills, such as the ability to process information automatically (processing speed), the ability to react and decide automatically (response speed), attention, calculation, imagination, learning, memory, and visuospatial abilities [11].

For cognitive processing to occur, sensory inputs from the external environment are registered in primary sensory areas in both cerebral hemispheres, particularly in the temporal, parietal, and occipital lobes [12]. Cognitive processing requires a degree of alertness, attention and concentration. All input is screened in relation to previous experiences stored in the subject's memory, and then processed, with the left cerebral hemisphere predominantly processing verbal information, and the right hemisphere processing visuospatial information. New information proceeds to the highest level of central processing, which involves abstraction, concept formation, reasoning, and logical analysis and is performed throughout the cerebral cortex rather than in discrete areas [12]. Processing is followed by an appropriate response to the initial stimulus. Impairment at the highest level of central processing can affect a subject's ability to function in a logical and meaningful way, even though he or she may appear to be relatively intact [12].

Age and education are important predictors and modifiers of cognitive functions and so are often corrected for in standard neuropsychological tests [11]. Other variables that may affect cognitive function, but are more difficult to correct for, include depression, anxiety, pain, fatigue, and hemoglobin concentration.

Cognitive function can be assessed with neuropsychological tests. Most comprehensive neuropsychological batteries assess several domains, such as executive functioning, processing speed, memory, attention, verbal, and visual learning [11]. Self-reports are not valid assessments of cognition because they are affected by mood and fatigue [13,14]. Studies of women treated for breast cancer have detected alterations mostly in the frontal-subbreast cancerortical circuitry, which affects memory, processing speed, response speed, and attention [15]. Therefore, a test battery adequately sensitive to these domains is preferred. Further, the psychometric properties of test-retest reliability and the availability of alternative test forms are important [16].

1.3 REVIEW OF THE LITERATURE

The earliest evaluations of cognitive function after chemotherapy in patients with solid tumors appeared in 1974 [17,18]. Several other reports of cognitive impairment related to treatments of solid tumors, such as chemotherapy for non-small-cell lung cancer, have subsequently been published [19-22]. Larger studies have been conducted in the past 10 years, mostly among early-stage breast cancer patients because this group is large and has a high survival rate. Early studies of cognitive outcomes were primarily cross-sectional, although more recent studies have been prospective.

1.3.1 Cross Sectional Studies

The first investigations of cognitive function in women with breast cancer were cross-sectional studies conducted on women receiving adjuvant chemotherapy after a primary diagnosis and surgery of early breast cancer. These studies showed that the prevalence of impaired cognitive function was 28% to 75% among women with breast cancer treated with chemotherapy [23-26]. There were, however, marked methodological differences in that some studies used only cognitive screening measures and others used comprehensive neuropsychological test batteries. In addition, the definition of cognitive impairment was not consistent across these studies, which may in part explain the variability in the prevalence of cognitive impairment [15,27].

A few studies have also shown a dose-response relationship, with high-dose chemotherapy being associated with more severe cognitive impairment in women with breast cancer than in women treated with standard-dose chemotherapy [23,25,28].

The effect of adjuvant hormone therapy on cognition has also been investigated, primarily with cross-sectional studies. The most-cited study found no cognitive differences between former and non-users of selective estrogen receptor modulators (SERMs), but current users had lower mean scores on narrative writing tasks [29]. Further studies comparing SERM users to aromatase inhibitors users or to healthy controls found that both hormone therapies impaired verbal memory and processing speed [30-32].

Overall, the cognitive domains affected by adjuvant treatment included memory, response speed, and visuospatial skills [23-26,33,34].

1.3.2 Longitudinal Studies

To overcome the limitations of cross-sectional studies, longitudinal studies were started to evaluate cognitive performance [35-38]. In some prospective studies, between 20% and 30% of women with breast cancer had lower cognitive function than that in

healthy controls, even before starting adjuvant treatment [15,39], mostly in memory, attention, processing, and response speed [40].

Cognitive declines after diagnosis and before breast cancer surgery have been reported [13]. Women with breast cancer who underwent more invasive surgery for breast cancer exhibited greater cognitive decline than did women who underwent biopsy only [41]. Primary breast cancer surgery may adversely affect cognitive functions. Postoperative cognitive dysfunction has been documented in the early weeks after major noncardiac surgery, with the elderly being at risk [42]. Cardiac surgery can also be complicated by cognitive decline [43]. Neither regional nor general anesthesia affect the incidence of postoperative cognitive dysfunction [42].

Prospective studies have also reported that about 30% of women experience some cognitive decline after chemotherapy [13,44,45]. To determine whether persistent cognitive dysfunction is a consequence of chemotherapy in breast cancer patients, prospective studies have controlled for the effects of hormone therapy on cognition. However, these studies are few and contradictory [46-48]. For example, neuropsychological performance was worse in women receiving both chemotherapy and hormone therapy than in women treated with chemotherapy alone [34,38,44].

Many women who have undergone chemotherapy usually continue with hormone therapy for up to 5 years. The few studies of these women suggest that those undergoing both treatments had the most pronounced cognitive disruption [34,38,44], and the domains of cognition that are impaired appear to be related to the type of endocrine therapy [31].

1.3.3 Brain Imaging Studies

Neuroimaging studies using magnetic resonance imaging (MRI) and positron-emission tomography (PET) suggest that chemotherapy may be associated with both structural and functional changes in the brain. Studies using MRI have found reduced brain volumes and diffuse atrophy of the gray matter in the frontal and temporal brain regions [49-51] and of the white matter in the genu of the corpus callosum [52] over the course of chemotherapy. Partial recovery off gray matter density was noted one year after treatment. Women not exposed to chemotherapy or healthy controls had no such reductions in brain volume.

Studies with PET describe abnormal functional brain activation of glucose metabolism particularly in the frontal regions of women treated with chemotherapy.

These studies also suggested that women may be able to compensate for changes by recruiting additional brain structures to perform a given task [53].

The neuroprotective mechanisms of SERMs on brain function have also been assessed in two studies, one using both MRI and PET, which found no neuroprotective effects for Tamoxifen [62] and the other, using only PET, did [54,55].

1.3.4 Neurophysiological Studies

Electrophysiological studies using event-related potential and electroencephalography (EEG) have found neurophysiological differences between women receiving high or standard doses of chemotherapy and women with cancer but not undergoing chemotherapy. Alpha rhythms measured by event-related potentials and EEG varied by 0.05 Hz or greater. A variation of alpha rhythm $\geq$ 0.5 Hz, considered to be pathological in 42% (7/17) of women receiving high-dose chemotherapy, in 13% (2/16) of those receiving standard-dose therapy, and in none (0/14) of the women who received only local treatment [56]. Neuropsychological test results for alpha rhythms were not correlated with EEG results. Other studies have found that the P3 component (thought to be related to decreased activity in the norepinephrine system) was lower in women with breast cancer receiving chemotherapy than in women not receiving chemotherapy and that different chemotherapy regimens have different effects on brain functioning [57].

1.3.5 Studies using Genetic Techniques and Inflammatory Markers

Certain genetic variations may be associated with a higher risk of long-term cognitive changes [58]. Cancer survivors with at least one ε4 allele of the apolipoprotein E gene scored significantly lower in visual memory and spatial ability and lower in executive function, although not significantly so, then did survivors who did not carry an ε4 allele [59]. The results of this study support the hypothesis that the ε4 allele of the apolipoprotein E gene may be a potential genetic marker for increased vulnerability to chemotherapy-induced cognitive decline.

Elevated levels of pro-inflammatory cytokines may be related to cognitive problems [58]. In breast cancer patients, interleukin-6 (IL-6) levels increased after 3 days of treatment with paclitaxel but not in those treated with a combination 5-flourouracil, cyclophosphamide, and methotrexate [60]. Higher levels of IL-6 are associated with poorer executive function [61]. Menopausal women have altered cytokine levels,

including increased levels of IL-6 [62], which are also associated with difficulties in learning and memory [63].

1.3.6 Animal Studies

The effect of chemotherapeutic agents on cognitive functions has mostly been studied in breast cancer survivors, as mentioned above. However, animal studies have found acute chemotherapy-related deficits in tasks requiring involvement of the hippocampus and frontal system, as well as increased rates of cell death, and decreased rates of cell division in regions involved in neurogenesis, and progressive damage to white matter tracts. A Methotrexate-5-flourouracil [64] combination, a single dose of cyclophosphamide [65], and an Adriamycin-Cytoxan combination [66] can impair memory-related behavior in mice. Interestingly, the anti-oxidant N-acetyl cysteine prevented this chemotherapy-induced memory impairment, suggesting that some of the damage could be mediated by oxidative stress [66]. The chemotherapy agents were associated with increased cell death and decreased cell division in the subventricular zone, the dentate gyrus of the hippocampus (regions involved in neurogenesis), and in the corpus callosum in treated animals; neural progenitor cells and oligodendrocytes were particularly vulnerable [67,68]. Mice exposed to doxorubicin had increased cortical and hippocampal levels of tumor necrosis factor alpha (TNF-α), hyperactivation of microglia, oxidative stress, mitochondrial dysfunction, and increased neural cell death, despite the fact that doxorubicin was not detected in the brain [69,70]. These studies suggest that chemotherapy is neurotoxic in the brain and that inflammation may be mediate cognitive difficulties by reducing neural transmission.

1.4 QUALITY OF LIFE

Among quality-of-life studies in cancer patients, breast cancer has received the most attention for several reasons. The number of women with breast cancer is increasing, and early detection and treatment of breast cancer have improved life expectancy. Breast cancer also affects women's identities, making quality-of-life assessment vital for those who lose a breast[71].

After diagnosis, women with breast cancer have poorer physical functioning than do healthy controls [72,73]. At the end of primary treatment after surgery for breast cancer, women who had a mastectomy or received chemotherapy reported lower physical functioning than did women who had a sector resection or no chemotherapy [74]. Moreover, symptoms, including muscle stiffness, breast sensitivity, aches and pains,

daytime sleepiness, and difficulty concentrating, were common among patients in all groups and were associated with poor physical functioning and emotional wellbeing. Sexual functioning was worse for women who received chemotherapy than for those who did not, regardless of the type of surgery [75]. Although physical and treatment-related problems are frequent 1 month after breast cancer surgery, most women recover during the year after surgery [76]. Cross-sectional studies of long-term breast cancer survivors [77,78] and longitudinal studies of recently treated breast cancer patients [79,80] have suggested that adjuvant systemic treatment is associated with more severe and persistent physical symptoms.

Substantial evidence suggests that further medical workups after an abnormal screening mammogram have adverse psychological effects on women [81]. Psychological wellbeing is often impaired by anxiety and depression, which are the most important co-morbidities and treatment-related side effects cancer and its treatment, affecting one-third of cancer patients and persisting for months or years [82-85]. The cancer diagnosis, fears and concerns regarding death and disease recurrence, poorer body image, and altered perceptions of femininity, sexuality, and attractiveness can impair psychological wellbeing after treatment [71].

1.5 RETURN TO WORK

Breast cancer is the most common cancer among women in Sweden, and about half of affected women are of working age. Breast cancer may affect the ability to work during or after treatment. A recent Swedish study reported that 41 of 102 women treated for primary early-stage breast cancer still had not returned to work 10 months after surgery [86].

Work-related absences from sickness are high among women treated for breast cancer with chemotherapy [87], but the majority of these women continue working after treatment [88]. The factors associated with survivors' ability to continue to work include type of cancer, type of treatment, health status, level of education, and physical workload [88]. Work-related absences immediately after breast cancer surgery are also high and are associated with lower self-reported health status and younger age [89]. Among women one year after a diagnosis of breast cancer, treatment factors, such as axillary node dissection and chemotherapy; psychosocial factors, such as life satisfaction and coping; as well as high demands at work, were important in the decision to return to work [86,90].

Despite several studies on return to work (RTW) and dozens of clinical trials to

find better diagnostic methods and to detect the side effects of breast cancer treatment, the impact of cancer and its related factors on the ability to work after treatment needs to be further studied and identified. Side effects of breast cancer treatment include anxiety, depression, fatigue, cognitive dysfunction, post-traumatic stress symptoms, lymph edema, and chronic pain [87]. Women receiving adjuvant treatment [40], especially chemotherapy, often report difficulties with memory, attention, and executive function [2,3], which may be obstacles to returning to work. Moreover, breast cancer survivors who had less pain, less depression, and less anxiety reported a higher quality of life [91] and were more likely to return to work earlier.

In Sweden, physicians assess a patient's functional capacity and ability to work. They record the results of this assessment and their reasons for recommending continued sick leave in a medical certificate that is part of the patient's medical record. These assessments may also provide insight into what factors are associated with delayed RTW.

2 AIMS

Paper I: To determine whether a diagnosis of breast cancer and the subsequent sector resection or mastectomy affects cognitive functions in women.

Paper II: To determine whether measures of cognitive function change in women with early-stage breast cancer after surgery and adjuvant chemotherapy, adjuvant hormone therapy, or no adjuvant medical therapy and whether these measures differ from those of healthy women.

Paper III: To determine the impact of breast cancer diagnosis and its treatment on quality of life, depression, and anxiety in women with newly diagnosed breast cancer.

Paper IV: To identify any associations between cognitive, psychosocial, somatic, and treatment factors with RTW among women treated for early-stage breast cancer. Further, to determine any relationships between objective measures of these factors and oncologists' opinions in the medical certificate for justifying reduced work capacity in women who had not yet returned to work.

3 MATERIAL AND METHODS

3.1 PARTICIPANTS

3.1.1 Patient Cohort (study I and III)

From September 2006 to March 2009, we approached 256 consecutive women from the mammography screening program at Stockholm South General Hospital who were reassessed for breast cancer as a result of a positive radiographic finding. Women were enrolled after oral and written consent was obtained. The study was approved by the ethics committee of the Karolinska Institute.

On their first assessment visit, all women completed a questionnaire asking for information regarding social status, work status, menopause status, and current and previous health conditions. We excluded women with a history of malignancy, with a past or current neurological or psychiatric disorder (defined according to International Statistical Classification of Diseases and Related Health Problems), or with a history of chemotherapy, cranial radiotherapy, bone marrow transplantation, or severe head trauma.

Enrolled women were divided into two main groups: those whose follow-up biopsies indicated breast cancer and a control group whose follow-up biopsies did not.

3.1.2 Patient Cohort (study II)

The breast cancer group consisted of women with early-stage breast cancer (ductal carcinoma in situ, stage 1 or 2). All enrolled women with breast cancer underwent surgery. All women with breast cancer were treated at the Department of Oncology, Karolinska University Hospital/Stockholm South General Hospital.

Within the breast cancer group, we identified three subgroups: a group of women who received adjuvant chemotherapy, a group who received adjuvant hormonal therapy, and a group who received no adjuvant medical therapy.

After baseline assessment, two women with breast cancer were excluded; one was diagnosed with rheumatoid arthritis and the other one received neo-adjuvant chemotherapy.

3.1.3 Patient Cohort (study IV)

For this study, we assessed a subset of the larger sample of women aged 40 to 64 years who reported having worked part-time or full-time before their original diagnosis and who had received adjuvant therapy.

3.1.4 Clinical Variables

Information on clinical variables—menopausal status; tumor characteristics, including stage, grade (Elston-Ellis), hormone receptors (estrogen receptor, progesterone receptor), HER-2 receptor, methods of surgery, and adjuvant treatment—was obtained from the patient's questionnaire, medical record, and pathology reports.

3.2 TESTING PROCEDURE

3.2.1 Testing Procedure (Studies I through III)

All women completed a web-based battery of neuropsychological tests at the Department of Oncology, Karolinska University Hospital, in Swedish, mostly between noon and 7 pm. A trained supervisor was available in the room to assist them. Women were tested four times (T): T1, at enrollment (a baseline measurement before reassessment results and diagnosis); T2, after surgery (about 2 months after diagnosis but before beginning adjuvant therapy); T3, after adjuvant therapy (about 8 months after diagnosis, which was about 1 month after completion of chemotherapy and about 6 months after start of hormone therapy); and T4, 4 months after the completion of adjuvant chemotherapy, or about 11 months after diagnosis. Healthy women were tested at the same intervals: after enrollment (before reassessment results and diagnosis) and at 2, 8, and 11 months after enrollment.

At each of the four test sessions, anxiety, depression, and quality-of-life were measured, and blood samples were obtained for routine measurements of thyroid function, hemoglobin count, and menopausal status.

3.2.2 Testing Procedure (Study IV)

For this study, we used the test results at two times, T3 and T4: about 8 months after diagnosis, which was 1 month after the completion of chemotherapy or 6 months after the start of hormonal therapy and about 11 months after diagnosis.

3.3 MEASUREMENTS

3.3.1 Assessment of Cognitive Function (studies I, II, and IV)

The women completed the Headminder Web-based neuropsychological battery Cognitive Stability Index, administered in Swedish [92], which provides objective measures of attention, memory, response speed, and processing speed. The Index was designed to monitor cognitive status in healthy, at-risk, and affected populations. It is designed primarily for use in prospective studies and consists of a series of repeatable neurocognitive subtests [93]. The 10 subtests assessed the above-mentioned four cognitive domains. These four domains have been validated against several traditional neuropsychological tests and have reliable psychometric properties [92].

Response speed, is correlated with Trail Making A and B (tests of visual attention and task switching; r = 0.73, r = 0.74, respectively). Processing speed is correlated with the Symbol Digit Modalities Test (a test of executive functions, such as problem solving, planning, organizational skills, selective attention, inhibitory control, and some aspects of short term memory [11]; r = 0.58), and the Symbol Search Test (a measure of intelligence [11]; r = 0.65). Memory is correlated with the Buschke Selective Reminding Test (a test for verbal memory and immediate recall [11]; r = 0.52). Attention is correlated with Digit Span (a test for short-term memory [11]; r = 0.62). Test-retest reliability between the first and second assessment ranged from 0.68 to 0.80, with significant practice effects seen only in processing speed [93]. No keyboard skills are required. The test takes 30 minutes to complete.

Higher summary scores for attention and memory and lower summary scores for processing speed and response speed indicate higher levels on their respective domains.

3.3.2 Assessment of Depression and Anxiety (studies I through IV)

Depression and anxiety were assessed at each test session with the Swedish versions of the Beck Depression Inventory, Second Edition (BDI-II), and the Beck Anxiety Inventory (BAI) [94,95]. The BDI-II questionnaire contains 21 items scored on a scale of 0 to 3. Total scores are interpreted as follows: 0 to 13, no to minimal depression; 14 to 19, mild depression; 20 to 28, moderate depression; and 29 to 63, severe depression. The BAI questionnaire also contains 21 items scored on a scale of 0 to 3. Total scores are interpreted as follows: 0 to 7, minimal anxiety; 8 to 15, mild anxiety; 16 to 25, moderate anxiety; and 26 to 63, severe anxiety. Scale scores on both inventories were analyzed as continuous measures. Women with raw scores of 15 or

higher on either the BDI-II or the BAI were classified as clinically distressed and those with scores below 15 were classified as healthy.

3.3.3 Assessment of Quality of Life (studies I through IV)

We assessed quality of life with the Swedish version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30) [96], a standardized and validated instrument that measures quality of life in cancer patients in clinical trials. It consists of 30 items measuring 5 functional scales (physical, role, cognitive, emotional, and social functioning), 9 symptom scales (fatigue, pain, nausea-vomiting, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and one global quality-of-life scale [97].

Women with breast cancer were also assessed with the EORTC QLQ Breast Cancer Module (QLQ BR-23), a validated instrument for measuring quality of life among breast cancer patients in various disease stages and undergoing various treatments [98]. The 23 QLQBR-23 items assess 4 functioning scales (body image, sexual function, sexual satisfaction/enjoyment, and future perspective) and 4 symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, and reaction to hair loss).

Scores for each scale range between 0 and 100. For scales evaluating global health and function, higher scores represent higher functioning and better health. For scales evaluating symptoms, higher scores reflect more symptoms and more severe illness.

3.3.4 Assessment of Comments in the Medical Certificate (study IV)

Information from the medical certificate regarding RTW was collected at both T3 (after adjuvant therapy) and T4 (11 months after diagnosis) and additionally at 18 months after diagnosis. Reasons regarding the patient's ability to return to work were categorized as 1) reduced general condition of health (a state of lower physical, mental, or social wellbeing); 2) somatic signs and symptoms (lymphedema, neuropathy); 3) psychological (depression and anxiety); 4) cognitive impairment; and 5) climacteric complaints (hot flushes or dryness).

4 RESULTS AND DISCUSSION

My interest in studying the effects of breast cancer diagnosis and treatment on cognitive functions began 7 years ago, when several of my patients at the outpatient department reported difficulties with memory, attention, and concentration during or after adjuvant treatment for breast cancer. These women related their symptoms to the beginning of adjuvant treatment and wondered whether these symptoms were side effects of the treatment. Unfortunately, I could not confirm whether or not the symptoms were treatment-related side effects. A literature search quickly revealed that this question was not well studied.

A growing body of literature suggests that adjuvant therapy for breast cancer may be associated with subtle impairments in both cognition and quality of life. The first investigations were cross-sectional and found that the prevalence of cognitive impairment ranged from16% to 75% [24,28,35,99]. However, these studies were cross-sectional, lacked baseline testing, and involved small samples. (In fact, we found no published studies that assessed baseline cognitive status before breast cancer diagnosis.) Later longitudinal studies found that 20% to 30% of women with breast cancer had lower cognitive function than did healthy controls, even before starting adjuvant treatment [15,39]. However, these studies also found that treatment can lower [100], not affect, or even improve cognitive function [100,101]. Thus, differences in design and methodology mean that these results need to be interpreted cautiously.

4.1 PATIENT CHARACTERISTICS

Of the 256 women eligible to participate in the study, 146 completed the first round of testing and 121 completed the fourth (Figure 1).

4.2 DEMOGRAPHIC CHARACTERISTICS

Healthy women were a mean of 8 years younger than women with breast cancer (51 vs. 59 years; $P<0.01$), probably as a result to the County of Stockholm's decision to screen all women aged between 40 and 50 years, which lead to more re-assessment of healthy women in this age group.

The two groups had similar proportions of women with more than 12 years of school and those with less than 12 years. Moreover, an age-adjusted analysis found no significant difference in education levels among the three adjuvant treatment groups and healthy controls. However, the non medically treated group was not as

homogenous in its age-adjusted education level as other groups (Figure 2). About 70% of women in both groups were married or cohabiting.

Figure 1. Disposition of 146 women in a test of cognitive function after 1) notification of a positive mammographic screening test, 2) after the diagnosis was ruled out or after sector resection or mastectomy, 3) after 6 months or after adjuvant treatment, and 4) after an additional 3 months follow-up.

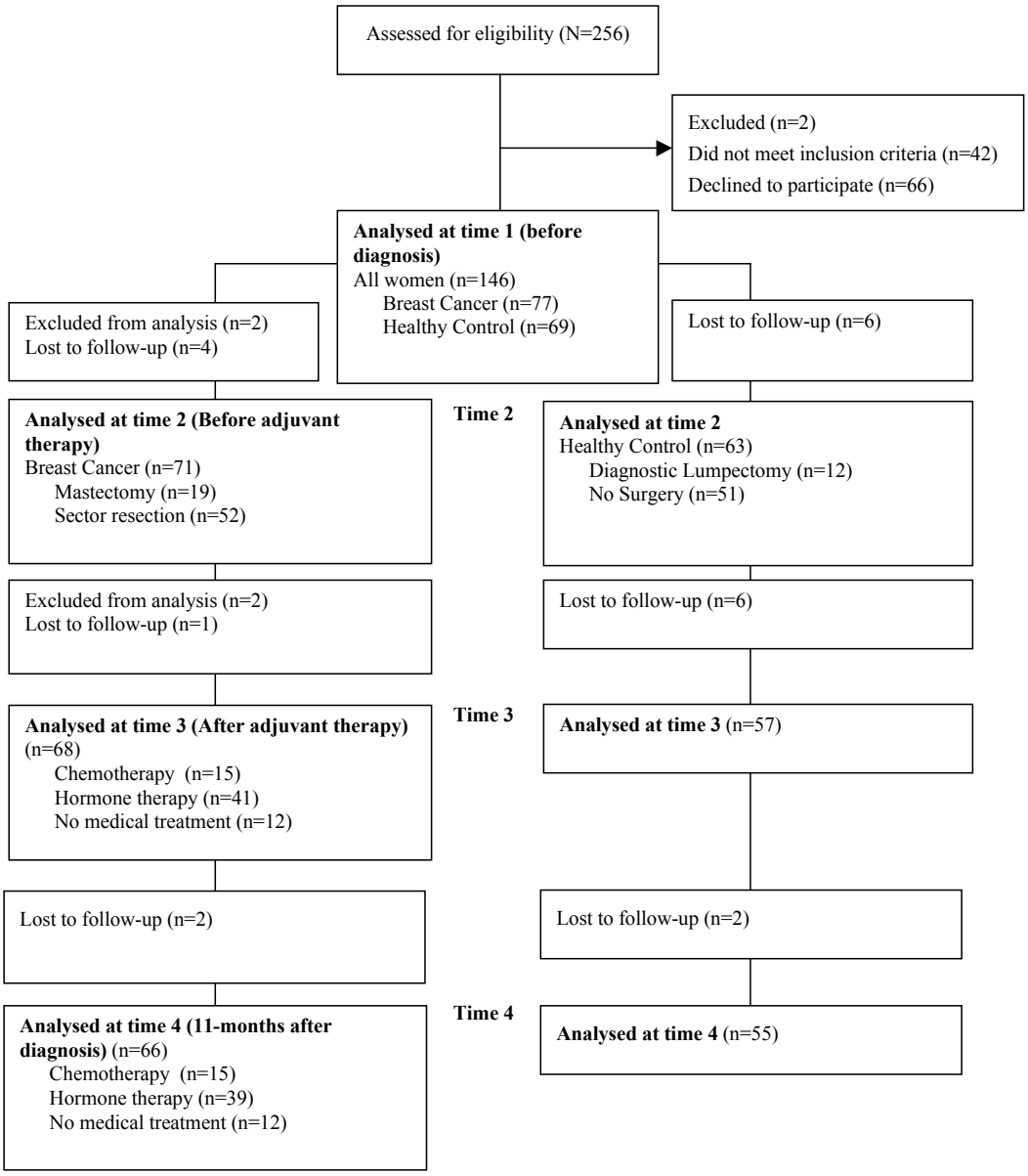
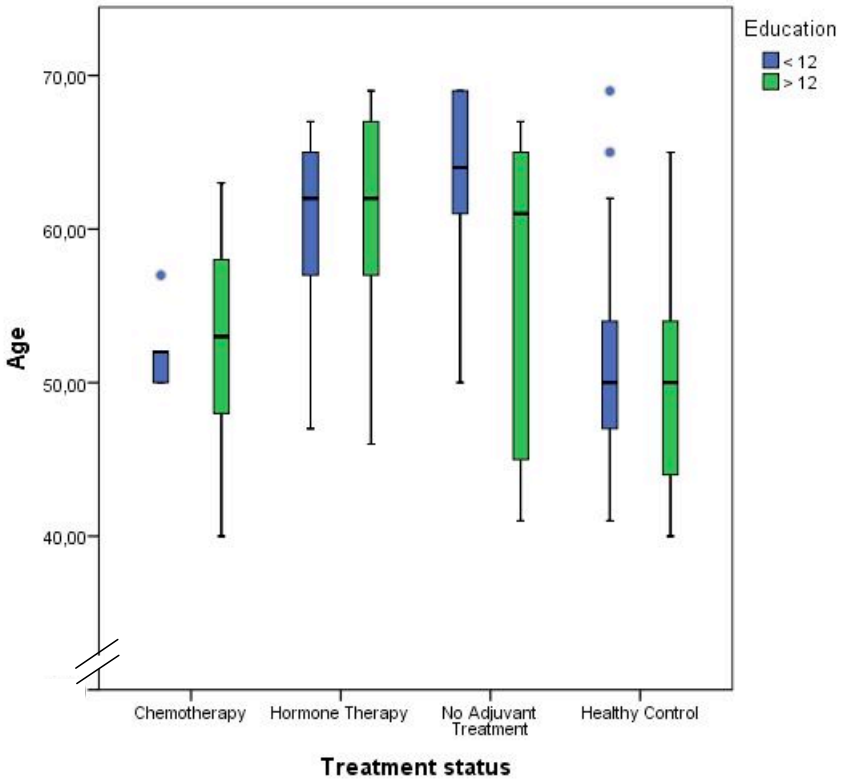


Figure 2. Age and education of 146 women screened for breast cancer, by eventual diagnoses and type of adjuvant treatment.



4.3 TUMOR AND TREATMENT CHARACTERISTICS

Of the 77 women with breast cancer, 12 (16%) had stage 0 breast cancer and did not receive any adjuvant medical treatment, 41 (53%) had stage 1 cancer and mostly received hormone therapy, and 24 (31%) had stage 2 breast cancer (Table 2).

Table 2. Tumor Characteristics of 77 Women with Early Breast Cancer

Tumor characteristic	Chemotherapy (n = 18) n (23%)	Hormone Therapy (n = 45) n (59%)	No Adjuvant Medical Therapy (n = 14) n (18%)
Breast cancer stage			
0	0	1 (2)	11 (79)
1	3 (17)	35 (78)	3 (21)
2	15 (83)	9 (20)	0
Hormone Receptor status			
Positive	17 (94)	45 (100)	2 (14)
Negative	1 (6)	0	12 (86)
Her2neu Receptor status			
Positive	6 (33)	0	0
Negative	12 (67)	45 (100)	14 (100)
Elston Ellis grade			
1	2 (11)	23 (51)	0
2	7 (39)	17 (38)	2 (14)
3	9 (50)	4 (9)	1 (7)

Women with breast cancer were divided into three subgroups on the basis of the adjuvant therapy, the second round of testing. Chemotherapy was indicated in 17 women, of whom 9 received intravenous FEC (5-fluorouracil 600 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 600 mg/m^2 every 3 weeks for 6 cycles) and 8 received intravenous TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 600 mg/m^2 every 3 weeks for 6 cycles). All women were offered standard antiemetic treatment. Hormonal treatment was indicated in 45 women, 33 of whom were prescribed tablet Tamoxifen 20 mg/day and 12 of whom were prescribed tablet Arimidex 1 mg/day. Finally, 14 did not require adjuvant treatment.

Of the 59 women undergoing radiotherapy to the chest wall or residual breast, with or without exposure to the regional lymph nodes, 17 were in the chemotherapy group, 34 were in the hormone group, and 8 did not receive adjuvant therapy.

The hormone group had received treatment for 6 months and had completed radiotherapy if needed after surgery. None in the chemotherapy group had started

hormone treatment or radiotherapy after surgery. At 11 months of follow-up, the chemotherapy group had completed radiotherapy and started hormone treatment (n =17), with or without trastuzumab (n= 6) if needed.

4.4 PAPER I

The aim of the study was to determine the effect of breast cancer diagnosis and surgery on cognitive function. Cognitive decline before initiation of adjuvant treatment has been reported [13,15,39], and a diagnosis of breast cancer has been suggested as a potential risk factor for cognitive impairment.

The groups differed significantly in response speed and processing speed, at baseline, before diagnosis. Women undergoing surgery for breast cancer showed no significant changes in memory, attention, response speed, or processing speed after treatment in either the adjusted or the unadjusted models. The adjusted covariates were age, education level, pain, B-hemoglobin, depression, and anxiety. Healthy women whose follow-up biopsies ruled out breast cancer, improved significantly in attention ($P = 0.02$) and in processing speed ($P < 0.02$) after surgery. After primary treatment, women with breast cancer differed significantly from healthy controls only in attention after adjusting for confounders ($P = 0.04$; Figure 3).

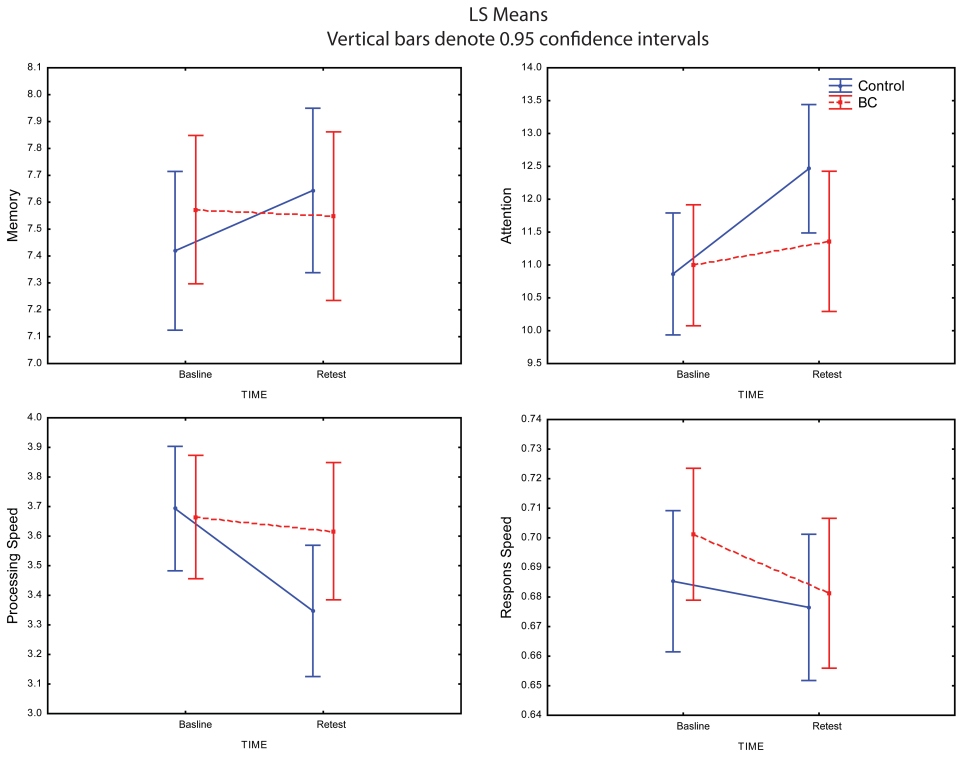
Of the 77 women with breast cancer, 55 had sector resection and 22 had mastectomy with sentinel node dissection, with or without axillary dissection (Figure 1). To determine whether more invasive surgery adversely affected cognition, we took into account type of surgery in a separate model because diagnostic lumpectomy was also performed in 13 healthy controls. Scores for attention and processing speed were lower, but not significant so, in women undergoing more invasive surgery (mastectomy) than in other women (Figure 4).

Our sample was divided almost equally between women with high and low levels of education, which is an important predictor of cognitive functions in healthy individuals. As did we, Lezak [11] reported that higher education level was related to better performance on objective measures, and we found that women with breast cancer and lower education levels showed a greater propensity for cognitive decline, although the decline was not statistically significant. One should consider the impact of lower education level on cognitive functions in women with breast cancer before starting treatment.

We did not correct for practice effects in our analyses. Relatively small improvements in test results at the second session are often caused by an increased

knowledge of what to expect on the test. However, lack of improvement on some tasks after repeated testing may indicate pathology [40,102]. Our results showed no overall improvement in cognitive functions in breast cancer patients after surgery. The lack of an expected practice effect among breast cancer patients may actually indicate a possible deficit. Therefore, it appears that a subgroup of breast cancer patients may be vulnerable to cognitive decline, which is consistent with other findings [13,41].

Figure 3. The unadjusted slopes of four neuropsychological domains by group and across time points. Higher scores for attention and memory indicate higher functioning. Lower scores for processing and response speed indicate higher functioning.

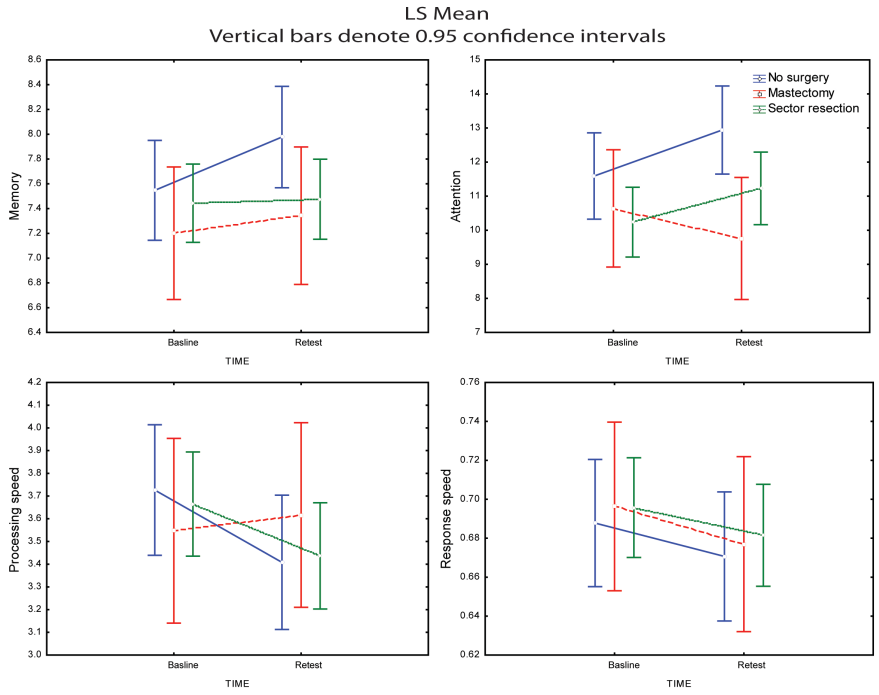


We found that attention significantly improved over 2 months time period for healthy women but not for those with breast cancer. This difference may be explained by diagnosis- and surgery-related, stress-response symptoms among breast cancer patients and stress-relief among healthy women. Scores on attention and working memory can be lower for women with breast cancer after surgery than for healthy controls [39,103]. Breast cancer diagnosis and surgery can obviously be traumatic, given

the threat to life and bodily integrity and the experience of disfiguration and disability. In turn, these posttraumatic symptoms may precede cognitive compromise and have been identified in some breast cancer survivors [104].

We found no relationship between cancer diagnosis and cognitive functions, depression, anxiety, or quality of life. Mean BDI-II and BAI scores indicate that neither group was distressed before diagnosis or after surgery. Quality of life scores, including participants' self-reported cognitive problems, did not change significantly during the study.

Figure 4. The unadjusted slops of four neuropsychological domains by surgery group. Higher scores for attention and memory indicate higher functioning. Lower scores for processing and response speed indicate higher functioning.



4.5 PAPER II

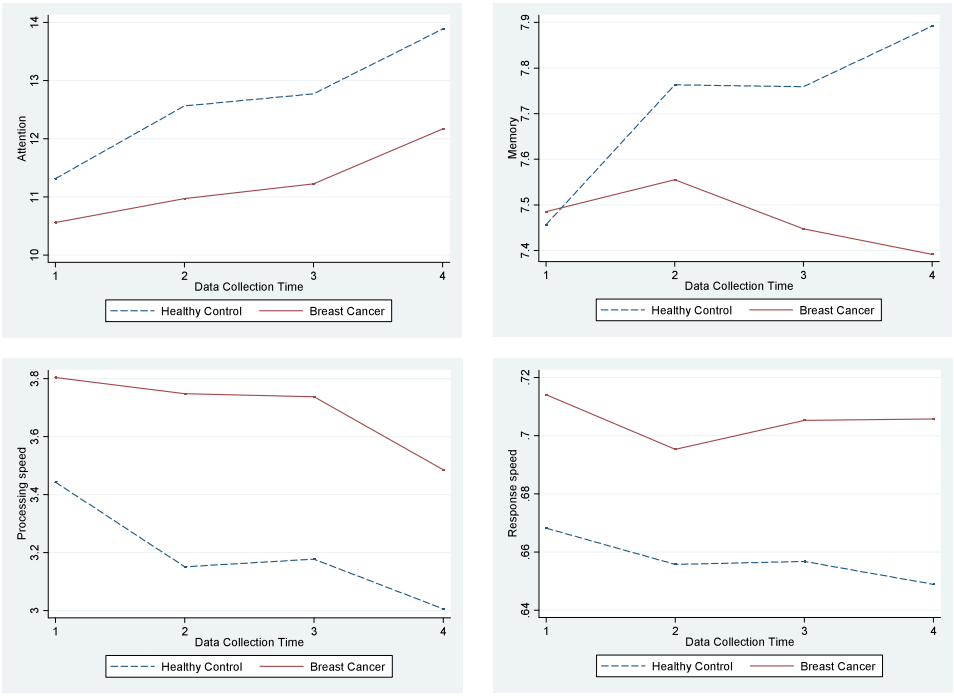
The aim of the study was to determine the effects of adjuvant therapy on cognitive function over time in women with early breast cancer and to determine whether the cognitive scores differed from those of healthy women.

Our results showed that scores for memory, attention, processing speed, and response speed changed among women with early breast cancer and healthy controls

over the study period. Further, healthy controls almost always performed better than did the women with breast cancer, on all four cognitive domains. Women with breast cancer in the youngest tertile (40 to 50 years old) performed better on all four domains than did older women with breast cancer.

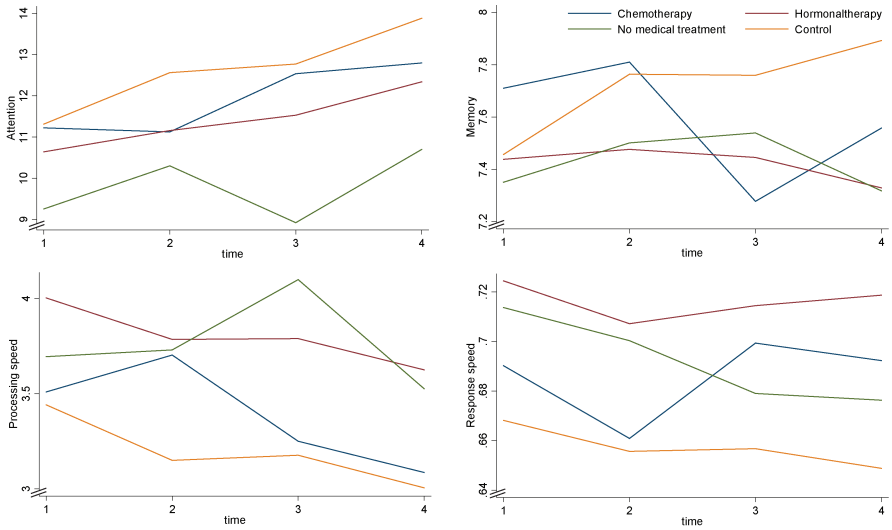
Women with cancer improved in response speed (P = 0.004), processing speed (P < 0.01), and attention (P = 0.002) but not in memory (Figure 5). The change in the memory scores differed between women with breast cancer and healthy controls over time (P <0.01 for the interaction). The absence of the expected practice effect in memory in the breast cancer group compared to healthy controls may indicate a decline in memory [36,40,102]. The difference in memory scores between women with and without cancer (P = 0.04) was confirmed by taking the three breast cancer treatment groups into account. Other studies have also found a cognitive decline after chemotherapy, with or without SERMs [35,44,105]. However, still other studies have found no change in neuropsychological performance among breast cancer patients receiving standard adjuvant treatment [101,106-108].

Figure 5. The unadjusted slopes of four neuropsychological domains by group and across time points. Higher scores for attention and memory indicate higher functioning. lower scores for processing and response speed indicate higher functioning.



We analyzed separately the three breast cancer treatment groups over time (Figure 6). In the chemotherapy group, response speed improved significantly after surgery (P <0.01) from before diagnosis but declined significantly (P < 0.01) 1 month after completing chemotherapy and remained low after 3 months of follow-up. Memory scores declined after completing chemotherapy (P < 0.01) but improved, although not significantly so, at the 11-month follow-up. This finding supports the result of another longitudinal study that evaluated 41 breast cancer patients receiving chemotherapy and 40 breast cancer patients receiving only radiotherapy, at baseline, post-treatment and at a 3-month follow-up [36,103].

Figure 6. The unadjusted slopes of four neuropsychological domains by group and across time points. Higher scores for attention and memory indicate higher functioning. Lower scores for processing and response speed indicate higher functioning.



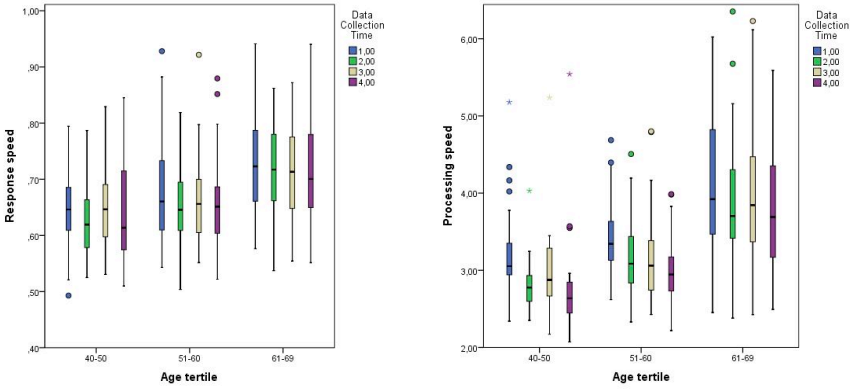
In the hormone therapy group, processing speed (P < 0.01) and attention (P < 0.01) scores were higher at 11months than they were before diagnosis. These results conflict with those of other studies, albeit cross-sectional, which reported that hormone treatment impairs processing speed [30,32,48]. We found also that after beginning hormone treatment, cancer patients' memory scores tended to be lower than those of healthy controls, suggesting possible age-, disease-, or host-related factors [41,109].

Women not receiving adjuvant medical therapy had mostly stage 0 breast cancer and were the only treatment group that improved in response speed (P = 0.02), a

finding consistent with a study showing that women with more severe disease (stages from I to III) had longer reaction times than did women with stage 0 disease and healthy controls [110]. Further, we found that processing speed declined after treatment but recovered significantly ($P < 0.01$) at the 11-month follow-up.

We analyzed potential associations between objective measures of cognitive performance and covariates. Age was associated with reduced processing and response speeds, which may be caused by several factors, such as volume loss in the brain and the loss of structural integrity in the white matter, particularly in the prefrontal cortex (Figure 7). Also, medical co-morbidities and reduced immunological function may be associated with cognitive decline [111]. Similarly, women with less education may be more at risk for impaired memory, attention, and processing speed (Figure 8).

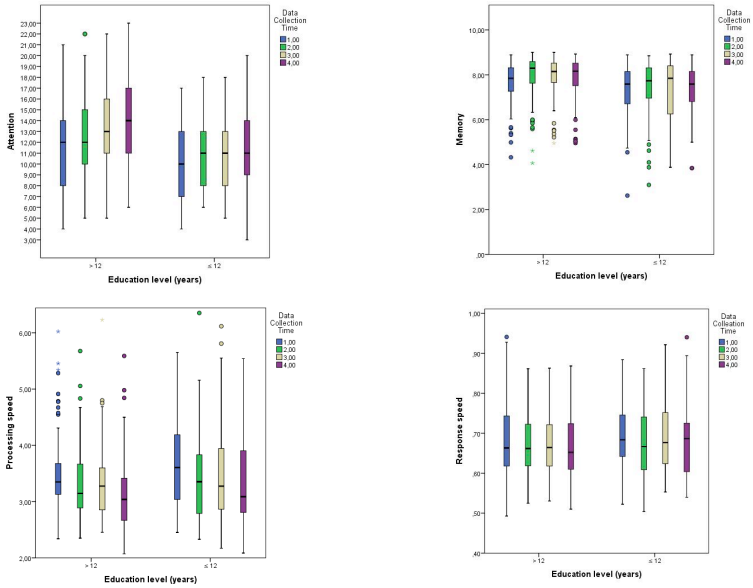
Figure 7. The Mean scores of two neuropsychological domains by age tertiles and across time points. Lower scores for processing and response speed indicate higher functioning.



As have other studies, we found no association between objective cognitive performance and depression or anxiety [112]. Also as in several other studies, we did not detect any association between neuropsychological test scores and subjective reports of cognitive function [28,34,113].

Further, hemoglobin counts, pain, and fatigue scores included in all models as time-varying covariates showed no main effects or interactions. Also, adding baseline domain scores, educational level, and age tertiles in all models showed that younger women had a significantly better performance only in memory over time.

Figure 8. Mean scores of four neuropsychological domains by education level and across time points. Higher scores for attention and memory indicate higher functioning. Lower scores for processing and response speed indicate higher functioning.



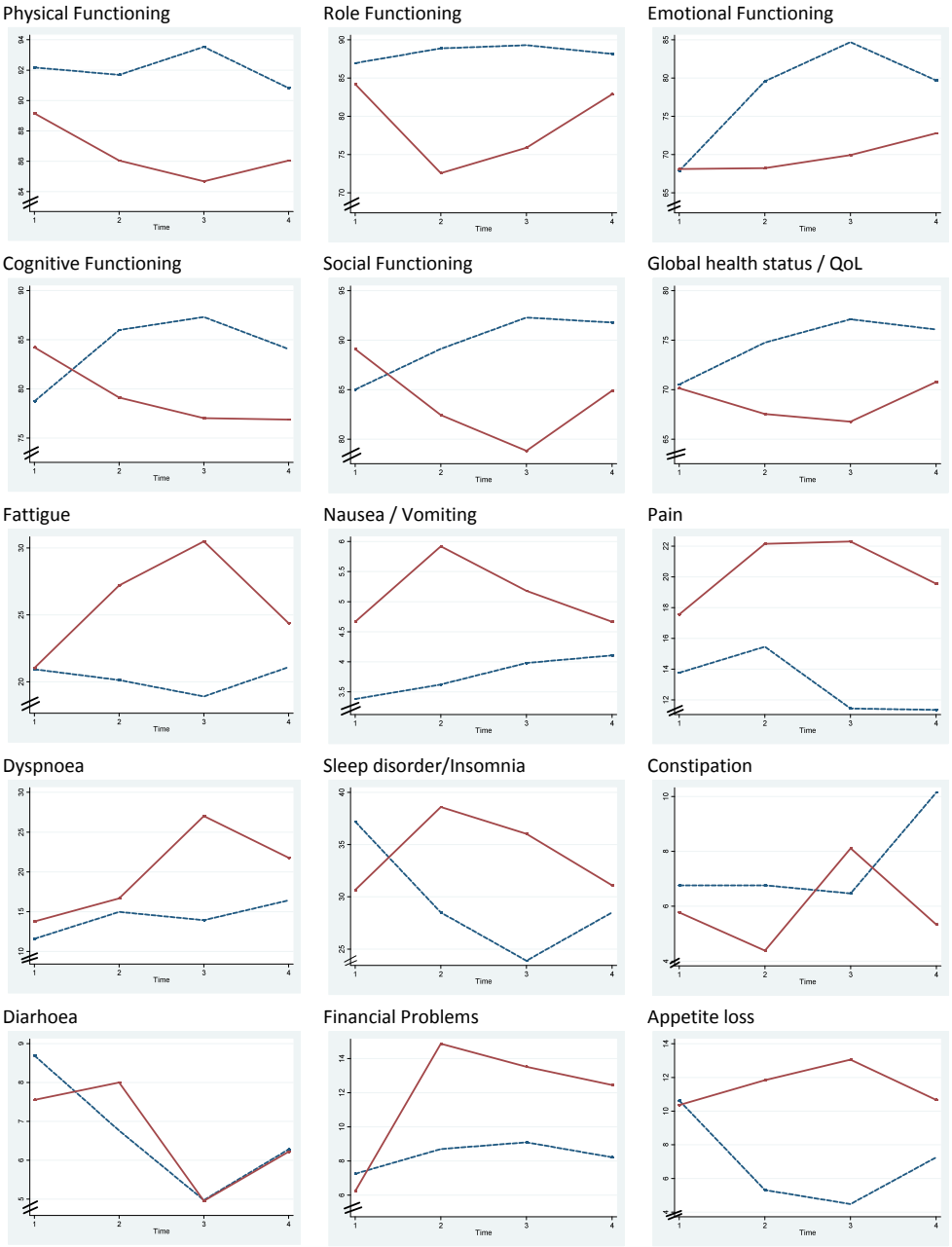
4.6 PAPER III

The aim of the study was to determine the impact of breast cancer diagnosis and its treatment on quality of life of women with newly diagnosed breast cancer. Our results showed that quality of life scores for all functional scales, global health status, fatigue, dyspnea, sleep disorders, and appetite loss differed significantly between groups over time.

Being recalled for further investigation after an abnormal screening mammogram is stressful for many women [81]. We found evidence of this stress in our study when, during re-assessment, women's psychological wellbeing and emotional functioning were mildly impaired.

Shortly after diagnosis and after surgery, women with breast cancer reported poorer quality of life and psychological wellbeing than did healthy controls (Figure 9). Surgery, irrespective of surgery type, impairs quality of life and can increase depression and anxiety, mostly as a result of side effects, such as pain and fatigue. [114]. We found that women with breast cancer consistently reported having pronounced arm and breast symptoms shortly after surgery and that persisted over 11 months time.

Figure 9. Mean quality-of-life scores for 76 women with breast cancer (red lines) and 69 healthy controls (blue lines), from before cancer diagnosis to about a year later. For scales evaluating global health and function, higher scores represent higher functioning and better health. For scales evaluating symptoms, higher scores indicate more symptoms and more severe illness.



Women with breast cancer reported poorer postsurgical physical, role, cognitive, and social functioning and poorer global health status, 8 months after diagnosis. However, by the end of the study, mean scores in almost all QLQ scales, except cognitive functioning, had improved (Figure 9). Emotional functioning improved in both groups over time, a finding consistent with studies showing that emotional problems declined after the start of treatment [115]. These changes may reflect stress relief and that women have learned how to cope with their cancer.

Women with breast cancer reported higher systematic therapy side effects and hair loss after surgery, as a result of treatment over time (effect size 14% and 11% respectively). Sexual functioning was reported to be low after surgery, and although it improved, it was still low at the last follow-up assessment. Other studies have also reported that sexual dysfunction occurs as a result of treatment-induced premature menopause [116]. Body image declined during the study, whereas marked arm and breast symptoms were always reported over time.

Mean scores for anxiety and depression did not differ significantly between groups at baseline. However, mean depression and anxiety scores differed between groups as a result of treatment over time (effect size 14% and 15%, respectively) and at most, only about 30% of women were clinically anxious or clinically depressed, postsurgical. Others have also report that psychological wellbeing is affected in one-third of cancer patients [82-84].

4.7 PAPER IV

The aim of the study was to determine whether cognitive changes, lower quality of life, and higher depression and anxiety scores affect return to work among women after treatment for breast cancer.

A subset of 44 women who received adjuvant therapy and were working before the study was selected; 29 who had returned to work and 15 who were still on sick leave.

Of the 17 women who completed adjuvant chemotherapy and the 8-month data collection process, all but 1 continued with adjuvant endocrine treatment. Moreover, at the time of 8-month data collection 20 women had received endocrine treatment for 6 months and had completed radiotherapy if needed. Adjuvant medical treatment was not indicated in 6 women. Of the 32 women undergoing radiotherapy to the chest wall or residual breast, with or without exposure to the regional lymph nodes, 17 were in the

chemotherapy group, 10 were in the hormone group, and 5 did not receive adjuvant medical therapy.

At the 8- and 11-month data collection times, scores on the four cognitive domains did not predict RTW. Women with more advanced disease, who received chemotherapy, and whose overall quality of life was lower took longer to return to work. Lower scores on physical, social, and role functioning, and also lower scores on body image and future perspective were also associated with RTW**.** More severe systemic therapy side effects, sleep disturbance, dyspnea, breast symptoms, and arm symptoms likewise prolonged RTW (Table 3). Others have also reported that women with breast cancer treated with chemotherapy do not return to work as soon as women not treated with chemotherapy [79,86,117].

We found that 32% (14/44) of women had not returned to work 11 months after breast cancer diagnosis and that 9% (4/44) had not returned to work 18 months after breast cancer diagnosis. Johnsson et al. [84,] found that 41 of the 102 women they studied had not returned to work after 10 months, and Balak et al. [116] found that 35% of the 72 women they studied also did not returned to work after 12 months. In our study, women on sick leave at baseline had more severe and persistent physical and psychosocial symptoms, which improved over the 11months of follow-up, consistent with other studies [79]. We also found that early RTW was associated with higher physical and social function and less severe treatment-related symptoms.

Women on sick leave were more likely to be more depressed and anxious than were working women. In contrast, working women were not psychologically distressed, had an overall better quality of life, and reported lower treatment-related side effects than did women on sick leave.

At the 8-month data collection point, the most common reasons in the medical certificate for justifying continued sick leave were lower general condition of health and somatic symptoms. Although most women, independently of the type of adjuvant treatment, had regained their general health at the 11-month follow-up appointment**,** somatic symptoms persisted among those reporting them at baseline. Statements on the medical certificate 8 and 11 months after breast cancer diagnosis were related to systemic side effects and support our finding that treatment-related symptoms were the main predictors of RTW.

Table 3. A Pairwise Comparison and Association between Quality of Life and Tumor Characteristics among Breast Cancer Treated women Returning to Work (n=29) vs. Remaining on Sick Leave (n=15).

	Adjusted * Odds ratio		**Unadjusted* Odds ratio**	
Variable	**95% CI**	**P**	**95% CI**	**P**
Physical functioning	0.83	<0.001	0.90	<0.001
	0.74 to 0.90		0.84 to 0.94	
Role functioning	0.94	<0.001	0.95	<0.001
	0.91 to 0.96		0.92 to 0.97	
Social Functioning	0.96	<0.001	0.97	0.01
	0.93 to 0.99		0.95 to 0.99	
Dyspnea	1.07	<0.001	1.03	<0.001
	1.04 to 1.11		1.01 to 1.06	
Sleep disturbance	1.02	<0.001	1.02	0.01
	1.01 to 1.05		1.01 to 1.03	
Body image	0.92	<0.001	0.95	<0.001
	0.87 to 0.96		0.92 to 0.97	
Future perspective	0.96	0.01	0.98	0.02
	0.93 to 0.98		0.96 to 0.99	
Systemic therapy side	1.07	<0.001	1.07	<0.001
effects	1.03 to 1.13		1.03 to 1.11	
Breast symptoms	1.03	0.03	1.02	0.04
	1.01 to 1.07		1.00 to1.05	
Arm symptoms	1.06	<0.001	1.04	<0.001
	1.02 to 1.10		1.02 to 1.07	
Her 2-positive	10.42	0.01	5.05	0.01
	2.19 to 65.32		1.43 to 20.65	
Elston grade	3.64	<0.001	2.63	<0.001
	2.01 to 7.31		1.55 to 4.78	
Involved lymph	18.80	<0.001	12.80	<0.001
nodes	5.32 to 90.69		4.46 to 42.59	

* Population-average models from general estimating equations with and without adjustments for age, education, marital status, and work status at baseline.

5 CONCLUSIONS AND CLINICAL IMPLICATIONS

The work presented in this thesis provides insight into various effects of breast cancer diagnosis and treatment on cognitive functions, quality of life and womens´ ability to return to work, over an 11-month observational period.

In our first paper, we found that cognitive functions before diagnosis did not change after breast cancer diagnosis and subsequent surgery. However, we did find that having a mastectomy and a lower education level were associated with greater propensity for cognitive decline, which needs to be further investigated. Therefore, it appears that a subgroup of breast cancer patients may be vulnerable to cognitive decline.

In our second paper, we evaluated the same women and healthy controls 6 and 9 months later using the same neuropsychological test battery and questionnaires. We did not observe any major cognitive changes over time, but all women improved on most cognitive functions, except for memory. Our results suggest that 6 and 9 months after surgery, regardless of the type of adjuvant treatment received, memory scores were below baseline scores.

In our third paper, we found that breast cancer patients reported marked declines in their quality of life and psychological well being but, at the same time, showed no major reductions in attention, processing speed, or response speed. Global health status returned to baseline after 11 months. However, some women had sustained problems, such as poor body image and subjective cognitive function, that may require treatment to improve overall quality of life.

In our fourth paper, we found that women who had received chemotherapy, more advanced disease with lymph-node involvement, and positive HER-2 status were less likely to return to work at either 8 or 11 months after diagnosis. However, we found no association between objective cognitive function and return to work among women treated with chemotherapy.

We conclude that attention scores in breast cancer patients do not change after diagnosis and surgery. Subtle but clinically meaningful cognitive changes, particularly in memory, are related to time course and treatment. Moreover, the changes we found in cognitive function are consistent with those reported by breast cancer survivors after adjuvant medical treatment, especially chemotherapy. Chemotherapy is associated with several other factors that reduce quality of life. We found that breast cancer surgery and adjuvant treatment, irrespectively of type, temporarily reduces health-related quality of

life and psychological wellbeing. However, independently of any adjuvant treatment, overall quality of life improves and most women eventually return to work in a few months.

In conclusion, older and less-educated women with breast cancer, who undergo mastectomy and receive adjuvant chemotherapy are at risk for cognitive decline. These women should, before starting treatment, complete the neuropsychological tests we used here. In this way, we can, in routine clinical practice, easily screen for women with these symptoms and identify any depression, anxiety, or cognitive impairment. We can use this knowledge to target support resources in a more efficient way. In the long run, this change in care should reduce sick leave time and accelerate the rehabilitation process.

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7 REFERENCES

1. Cancer incidence in Sweden 2009. Official statistics of Sweden (In Swedish: Cancerförekomst i Sverige 2009), The National Board of Health and Welfare, Stockholm, Sweden 2010.

2. Shilling V, Jenkins V: Self-reported cognitive problems in women receiving adjuvant therapy for breast cancer. Eur J Oncol Nurs 11:6-15, 2007.

3. Berglund G, Bolund C, Fornander T, et al: Late effects of adjuvant chemotherapy and postoperative radiotherapy on quality of life among breast cancer patients. Eur J Cancer 27:1075-1081, 1991.

4. Tabár L, Vitak B, Chen TH, et al: Swedish Two-County Trial: Impact of Mammographic Screening on Breast Cancer Mortality during 3 Decades. Radiology 260:658-663, 2011.

5. Halsted W: The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. Ann Surg 20:497–5, 1894.

6. Benson J, Jatoi I, Keisch M, et al: Early breast cancer. Lancet 25:1463-79, 2009.

7. Clarke M, Collins R, Darby S, et al: 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 randomised trials. Lancet 366:2087-2106, 2005.

8. Braun S, Vogl FD, Naume B, et al: A Pooled Analysis of Bone Marrow Micrometastasis in Breast Cancer. N Engl J Med 353:793-802, 2005.

9. Goldhirsch A, Wood WC, Coates AS, et al: Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 22:1736-1747, 2011.

10. Ravdin PM, Siminoff LA, Davis GJ, et al: Computer Program to Assist in Making Decisions About Adjuvant Therapy for Women With Early Breast Cancer. J Clin Oncol 19:980-991, 2001.

11. Lezak MD: Neuropsychological Assessment. New York., Oxford University Press, 2004, 4th ed.

12. Reitan R, Wolfson D: The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation. South Tucson, Neuropsychology Press, 1993, 2nd ed.

13. Hermelink K, Untch M, Lux MP, et al: Cognitive function during neoadjuvant chemotherapy for breast cancer. Cancer 109:1905-1913, 2007.

14. Bardwell WA, Natarajan L, Dimsdale JE, et al: Objective Cancer-Related Variables Are Not Associated With Depressive Symptoms in Women Treated for Early-Stage Breast Cancer. J Clin Oncol 24:2420-2427, 2006.

15. Correa DD, Ahles TA: Neurocognitive Changes in Cancer Survivors. Cancer J 14:396-400, 2008.

16. Wefel JS, Vardy J, Ahles T, et al: International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 12:703-708, 2011.

17. Weiss HD, Walker MD, Wiernik PH: Neurotoxicity of Commonly Used Antineoplastic Agents. N Engl J Med 291:75-81, 1974.

18. Weiss HD, Walker MD, Wiernik PH: Neurotoxicity of Commonly Used Antineoplastic Agents. N Engl J Med 291:127-133, 1974.

19. Kaasa S, Olsnes B, Mastekaasa A: Neuropsychological evaluation of patients with inoperable non-small cell lung cancer treated with combination chemotherapy or radiotherapy. Acta Oncol 27:241-6, 1988.

20. Oxman TE, Silberfarb PM: Serial cognitive testing in cancer patients receiving chemotherapy. Am J Psychiatry 137:1263-1265, 1980.

21. Silberfarb PM, Philibert D, Levine PM: Psychosocial aspects of neoplastic disease: II. Affective and cognitive effects of chemotherapy in cancer patients. . Am J Psychiatry 137:597–601, 1980.

22. Meyers CA, Abbruzzese JL: Cognitive functioning in cancer patients: Effect of previous treatment. Neurology 42:434-436, 1992.

23. Ahles TA, Saykin AJ, Furstenberg CT, et al: Neuropsychologic Impact of Standard-Dose Systemic Chemotherapy in Long-Term Survivors of Breast Cancer and Lymphoma. J Clin Oncol 20:485-493, 2002.

24. Wieneke MH, Dienst ER: Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. Psycho-Oncology 4:61-66, 1995.

25. Schagen SB, van Dam FSA, Muller MJ, et al: Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer 85:640-650, 1999

26. Downie FP, Mar Fan HG, Houédé-Tchen N, et al: Cognitive function, fatigue, and menopausal symptoms in breast cancer patients receiving adjuvant chemotherapy: evaluation with patient interview after formal assessment. Psycho-Oncology 15:921-930, 2006.

27. Shilling V, Jenkins V, Trapala I: The (mis)classification of chemo-fog – methodological inconsistencies in the investigation of cognitive impairment after chemotherapy. Breast Cancer Res Treat 95:125-129, 2006.

28. van Dam FSA, Schagen SB, Muller MJ, et al: Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst 90:210-218, 1998.

29. Paganini-Hill A, Clark L: Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. Breast Cancer Res Treat 64:165-76, 2000.

30. Jenkins V, Shilling V, Fallowfield L, et al: Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. Psycho-Oncology 13:61-66, 2004.

31. Schilder CM, Eggens PC, Seynaeve C, et al: Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: Cross-sectional findings from the neuropsychological TEAM-side study. Acta Oncol 48:76-85, 2009.

32. Bender CM, Sereika SM, Brufsky AM, et al: Memory impairments with adjuvant anastrozole versus tamoxifen in women with early-stage breast cancer. Menopause 14:995-8, 2007.

33. Kreukels BP, van Dam FSA, Ridderinkhof KR, et al: Persistent neurocognitive problems after adjuvant chemotherapy for breast cancer. Clin Breast Cancer 8:80 - 87, 2008.

34. Castellon SA, PA G: Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. J Clin Exp Neuropsychol 26:955-69, 2004.

35. Wefel JS, Lenzi R, Theriault RL, et al: The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma. Cancer 100:2292-2299, 2004.

36. Shilling V, Jenkins V, Morris R, et al: The effects of adjuvant chemotherapy on cognition in women with breast cancer--preliminary results of an observational longitudinal study. Breast 14:142-150, 2005.

37. Fan HGM, Houede-Tchen N, Yi Q-L, et al: Fatigue, Menopausal Symptoms, and Cognitive Function in Women After Adjuvant Chemotherapy for Breast Cancer: 1- and 2-Year Follow-Up of a Prospective Controlled Study. J Clin Oncol 23:8025-8032, 2005.

38. Bender CM, Sereika S, Berga S, et al: Cognitive impairment associated with adjuvant therapy in breast cancer. Psycho-Oncology 15:422-430, 2006.

39. Cimprich B, Reuter-Lorenz P, Nelson J, et al: Prechemotherapy alterations in brain function in women with breast cancer. J Clin Exp Neuropsychol 32: 324 - 331, 2009.

40. Vardy J, Wefel JS, Ahles T, et al: Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. Ann Oncol 19:623-629, 2008.

41. Wefel JS , Lenzi R, Theriault R, et al: 'Chemobrain' in breast carcinoma? Cancer 101:466-475, 2004.

42. Newman S, Stygall J, Hirani S, et al: Postoperative Cognitive Dysfunction after Noncardiac Surgery: A Systematic Review. Anesthesiology 106:572-590, 2007.

43. Sauër A-M, Kalkman C, van Dijk D: Postoperative cognitive decline. J Anesth 23:256-259, 2009.

44. Collins B, Mackenzie J, Stewart A, et al: Cognitive effects of chemotherapy in post-menopausal breast cancer patients 1 year after treatment. Psycho-Oncology 18:134-143, 2009.

45. Hurria A, Rosen C, Hudis C, et al: Cognitive Function of Older Patients Receiving Adjuvant Chemotherapy for Breast Cancer: A Pilot Prospective Longitudinal Study. J Am Geriatr Soc 54:925-931, 2006.

46. Jenkins VA, Ambroisine LM, Atkins L, et al: Effects of anastrozole on cognitive performance in postmenopausal women: a randomised, double-blind chemoprevention trial (IBIS II). Lancet Oncol 9:953-961, 2008.

47. Hermelink K, Henschel V, Untch M, et al: Short-term effects of treatment-induced hormonal changes on cognitive function in breast cancer patients. Cancer 113:2431-2439, 2008.

48. Collins B, Mackenzie J, Stewart A, et al: Cognitive effects of hormonal therapy in early stage breast cancer patients: a prospective study. Psycho-Oncology 18:811-821, 2009.

49. Saykin A, Ahles T, McDonald B: Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. Semin Clin Neuropsychiatry 8:201-16, 2003.

50. Inagaki M, Yoshikawa E, Matsuoka Y, et al: Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. Cancer 109:146-156, 2007.

51. McDonald B, Conroy S, Ahles T, et al: Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. Breast Cancer Res Treat 123:819-28, 2010.

52. Abraham J, Haut M, Moran M, et al: Adjuvant chemotherapy for breast cancer: effects on cerebral white matter seen in diffusion tensor imaging. Clin Breast Cancer 8:88-91, 2008.

53. Ferguson R, McDonald B, Saykin A, et al: Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. J Clin Oncol 25:3866-70, 2007.

54. Eberling JL, Wu C, Tong-Turnbeaugh R, et al: Estrogen- and tamoxifen-associated effects on brain structure and function. NeuroImage 21:364-371, 2004.

55. Ernst T, Chang L, Cooray D, et al: The Effects of Tamoxifen and Estrogen on Brain Metabolism in Elderly Women. J Natl Cancer Inst 94:592-597, 2002.

56. Schagen S, Hamburger H, Muller M, et al: Neurophysiological evaluation of late effects of adjuvant high-dose chemotherapy on cognitive function. J Neuroonco 51:159-65, 2001.

57. Kreukels BPC, Hamburger HL, de Ruiter MB, et al: ERP amplitude and latency in breast cancer survivors treated with adjuvant chemotherapy. Clin Neurophysiol 119:533-541, 2008.

58. Ahles T, Saykin A: Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 7:192-201, 2007.

59. Ahles T, Saykin A, Noll W, et al: The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psycho-Oncology 12:612-9, 2003.

60. Pusztai L, Mendoza TR, Reuben JM, et al: Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. Cytokine 25:94-102, 2004.

61. Meyers CA, Albitar M, Estey E: Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer 104:788-793, 2005.

62. Pfeilschifter J, Köditz R, Pfohl M, et al: Changes in Proinflammatory Cytokine Activity after Menopause. Endocr Rev 23:90-119, 2002.

63. Greendale GA, Huang MH, Wight RG, et al: Effects of the menopause transition and hormone use on cognitive performance in midlife women. Neurology 72:1850-1857, 2009.

64. Winocur G, Vardy J, Binns M, et al: The effects of the anti-cancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. Pharmacol Biochem Behav 85:66-75, 2006.

65. Reiriz A, Reolon G, Preissler T, et al: Cancer chemotherapy and cognitive function in rodent models: memory impairment induced by cyclophosphamide in mice. Clin Cancer Res 12:5000, 2006.

66. Konat G, Kraszpulski M, James I, et al: Cognitive dysfunction induced by chronic administration of common cancer chemotherapeutics in rats. Metab Brain Dis 23:325-33, 2008.

67. Dietrich J, Han R, Yang Y, et al: CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. J Biol. 5:22, 2006.

68. Han R, Yang Y, Dietrich J, et al: Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. J Biol. 7:12, 2008.

69. Tangpong J, Cole M, Sultana R, et al: Adriamycin-mediated nitration of manganese superoxide dismutase in the central nervous system: insight into the mechanism of chemobrain. J Neurochem. 100:191-201, 2007.

70. Joshi G, Aluise C, Cole M, et al: Alterations in brain antioxidant enzymes and redox proteomic identification of oxidized brain proteins induced by the anti-cancer drug adriamycin: implications for oxidative stress-mediated chemobrain. Neuroscience. 166:796-807, 2010.

71. Montazeri A: Health-related quality of life in breast cancer patients: A bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res 27:32, 2008.

72. Dorval M, Maunsell E, Deschênes L, et al: Long-term quality of life after breast cancer: comparison of 8-year survivors with population controls. J Clin Oncol 16:487-94, 1998.

73. Helgeson VS, Tomich PL: Surviving cancer: A comparison of 5-year disease-free breast cancer survivors with healthy women. Psycho-Oncology 14:307-317, 2005.

74. Ganz PA, Kwan L, Stanton AL, et al: Quality of Life at the End of Primary Treatment of Breast Cancer: First Results From the Moving Beyond Cancer Randomized Trial. J Natl Cancer Inst 96:376-387, 2004.

75. Ganz PA, Desmond KA, Belin TR, et al: Predictors of Sexual Health in Women After a Breast Cancer Diagnosis. J Clin Oncol 17:2371-2371, 1999.

76. Shimozuma K, Ganz PA, Petersen L, et al: Quality of life in the first year after breast cancer surgery: rehabilitation needs and patterns of recovery. Breast Cancer Res Treat 56:45-57, 1999.

77. Ganz PA, Desmond KA, Leedham B, et al: Quality of Life in Long-Term, Disease-Free Survivors of Breast Cancer: a Follow-up Study. J Natl Cancer Inst 94:39-49, 2002.

78. Ganz PA, Rowland JH, Meyerowitz BE, et al: Impact of different adjuvant therapy strategies on quality of life in breast cancer survivors. Recent Results Cancer Res. 152:396-411, 1998.

79. Ganz PA, Kwan L, Stanton AL, et al: Physical and Psychosocial Recovery in the Year After Primary Treatment of Breast Cancer. J Clin Oncol 29:1101-1109, 2011.

80. Jacobsen PB, Donovan KA, Small BJ, et al: Fatigue after treatment for early stage breast cancer. Cancer 110:1851-1859, 2007.

81. Gilbert FJ, Cordiner CM, Affleck IR, et al: Breast screening: the psychological sequelae of false- positive recall in women with and without a family history of breast cancer. Eur J Cancer 34:2010-2014, 1998.

82. Frick E, Tyroller M, Panzer M: Anxiety, depression and quality of life of cancer patients undergoing radiation therapy: a cross-sectional study in a community hospital outpatient centre. Eur J Cancer Care 16:130-136, 2007.

83. Maguire P: Managing psychological morbidity in cancer patients. Eur J Cancer 36:556-8, 2000.

84. Sukantarat K, Greer S, Brett S, et al: Physical and psychological sequelae of critical illness. Br J Health Psychol 12:65-74, 2007.

85. Fallowfield L: Assessment of quality of life in breast cancer. Acta Oncol 34:689-694, 1995.

86. Johnsson A, Fornander T, Rutqvist L-E, et al: Predictors of return to work ten months after primary breast cancer surgery. Acta Oncol 48:93-98, 2009.

87. Johnsson A, Fornander T, Olsson M, et al: Factors associated with return to work after breast cancer treatment. Acta Oncol 46:90-96, 2007.

88. Taskila T, Lindbohm ML: Factors affecting cancer survivors' employment and work ability. Acta Oncol 46:446-451, 2007.
89. Petersson L-M, Wennman-Larsen A, Nilsson M, et al: Work situation and sickness absence in the initial period after breast cancer surgery. Acta Oncol 50:282-288, 2011.

90. Johnsson A, Fornander T, Rutqvist L-E, et al: Work status and life changes in the first year after breast cancer diagnosis. Work 38:337-346, 2011.

91. Ferrans CE: Development of a quality of life index for patients with cancer. Oncol Nurs Forum 17:15-19, 1990.

92. Erlanger DM, Kaushik T, Broshek D, et al: Development and validation of a web-based screening tool for monitoring cognitive status. J Head Trauma Rehabil. 17:458-76, 2002.

93. Erlanger D, Feldman D, Kutner K, et al: Development and validation of a web-based neuropsychological test protocol for sports-related return-to-play decision-making. Arch Clin Neuropsychol 18:293-316, 2003.

94. Beck AT, Steer RA, Brown GK: Manual for beck depression inventory-ii. San Antonio, TX, 1996.

95. Beck AT, Epstein N, Brown G, et al: An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 56:893-7, 1988.

96. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. J Natl Cancer Inst 85:365-376, 1993.

97. Fayers PM, Aaronson NK, Bjordal K, et al: The EORTC QLQ-C30 Scoring Manual (3rd Edition), European Organization for Research and Treatment of Cancer. Brussels, 2001.

98. Sprangers MA, Groenvold M, Arraras JI, et al: The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 14:2756-2768, 1996.

99. Tchen N, Juffs HG, Downie FP, et al: Cognitive Function, Fatigue, and Menopausal Symptoms in Women Receiving Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol 21:4175-4183, 2003.

100. Schagen SB, Muller MJ, Boogerd W, et al: Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. J Natl Cancer Inst 98:1742 - 1745, 2006.

101. Jenkins V, Shilling V, Deutsch G, et al: A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Cancer 94:828-834, 2006.

102. Zehnder AE, Blasi S, Berres M, et al: Lack of Practice Effects on Neuropsychological Tests as Early Cognitive Markers of Alzheimer Disease? Am J Alzheimers Dis Other Demen 22:416-426, 2007.

103. Quesnel C, Savard J, Ivers H: Cognitive impairments associated with breast cancer treatments: results from a longitudinal study. Breast Cancer Res Treat 116:113-123, 2009.

104. Gurevich M, Devins GM, Rodin GM: Stress Response Syndromes and Cancer: Conceptual and Assessment Issues. Psychosomatics 43:259-281, 2002.

105. Bender CM, Sereika SM, Berga SL, et al: Cognitive impairment associated with adjuvant therapy in breast cancer. Psycho-Oncology 15:422-430, 2006.

106. Debess J, Riis J, Engebjerg M, et al: Cognitive function after adjuvant treatment for early breast cancer: a population-based longitudinal study. Breast Cancer Res Treat 121:91-100, 2010.

107. Mehlsen M, Pedersen AD, Jensen AB, et al: No indications of cognitive side-effects in a prospective study of breast cancer patients receiving adjuvant chemotherapy. Psycho-Oncology 18:248-257, 2009.

108. Schagen SB, Muller MJ, Boogerd W, et al: Change in Cognitive Function After Chemotherapy: a Prospective Longitudinal Study in Breast Cancer Patients. J Natl Cancer Inst 98:1742-1745, 2006.

109. Meyers CA, Byrne KS, Komaki R: Cognitive deficits in patients with small cell lung cancer before and after chemotherapy. Lung Cancer 12:231-235, 1995.

110. Ahles T, Saykin A, McDonald B, et al: Cognitive function in breast cancer patients prior to adjuvant treatment. Breast Cancer Res Treat 110:143-152, 2008.

111. Caserta MT, Bannon Y, Fernandez F, et al: Normal Brain Aging: Clinical, Immunological, Neuropsychological, and Neuroimaging Features, Int Rev Neurobiol 84:1-19, 2009.

112. Vardy J, Rourke S, Tannock IF: Evaluation of Cognitive Function Associated With Chemotherapy: A Review of Published Studies and Recommendations for Future Research. J Clin Oncol 25:2455-2463, 2007.

113. Stewart A, Collins B, Mackenzie J, et al: The cognitive effects of adjuvant chemotherapy in early stage breast cancer: a prospective study. Psycho-Oncology 17:122-130, 2008.

114. Nissen MJ, Swenson KK, Ritz LJ, et al: Quality of life after breast carcinoma surgery: a comparison of three surgical procedures. Cancer 91:1238-46, 2001.

115. Brandberg Y, Michelson H, Nilsson B, et al: Quality of Life in Women With Breast Cancer During the First Year After Random Assignment to Adjuvant Treatment With Marrow-Supported High-Dose Chemotherapy With Cyclophosphamide, Thiotepa, and Carboplatin or Tailored Therapy With Fluorouracil, Epirubicin, and Cyclophosphamide: Scandinavian Breast Group Study 9401. J Clin Oncol 21:3659-3664, 2003.

116. Grimison PS, Stockler MR: Quality of life and adjuvant systemic therapy for early-stage breast cancer. Expert Rev Anticancer Ther 7:1123-1134, 2007.

117. Balak F, Roelen C, Koopmans P, et al: Return to Work After Early-stage Breast Cancer: A Cohort Study into the Effects of Treatment and Cancer-related Symptoms. J Occup Rehabil 18:267-272, 2008.