Effects of tamoxifen and exemestane on cognitive functioning: a study in postmenopausal breast cancer patients
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Effects of tamoxifen and exemestane on cognitive functioning

a study in postmenopausal breast cancer patients

Christien Schilder
Effects of tamoxifen and exemestane on cognitive functioning

A study in postmenopausal breast cancer patients
The studies presented in this thesis were performed at the Division of Psychosocial Research and Epidemiology at the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital Amsterdam, in collaboration with the study coordinators of the Dutch part of the Tamoxifen and Exemestane Multinational (TEAM) trial.

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*The CCCA is one of eight Comprehensive Cancer Centers in the Netherlands. Its area is the north-western part of the Netherlands and involves 2,800.000 inhabitants, 16 general hospitals, two university hospitals and the Netherlands Cancer Institute. The comprehensive cancer centers (CCC’s) in the Netherlands have been founded to provide comprehensive and high-quality cancer care close to home for all cancer patients. The CCCA provides and coordinates a collaboration of all health care professionals and institutions involved in cancer and palliative care. The CCCA functions as a centre of knowledge and quality care that helps to improve cancer treatment, patient care and clinical research as well as prevention of cancer and decrease of cancer mortality.
Effects of tamoxifen and exemestane on cognitive functioning

A study in postmenopausal breast cancer patients

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Chapter 1

General Introduction
Chapter 1

General Introduction

Breast cancer is the most common malignancy in women in the Netherlands, with an incidence of 13,000 annually.\textsuperscript{1} Due to more effective treatment, earlier diagnosis, and the introduction of a nationwide screening program in 1990, the prognosis of breast cancer has improved substantially.

Systemic treatments for breast cancer

Systemic treatments such as chemotherapy and endocrine therapy play an important role in the treatment of breast cancer in addition to loco-regional treatments such as surgery and radiation. In postmenopausal women, approximately 75\% of the breast tumors are hormone sensitive.\textsuperscript{2} For hormone-sensitive breast cancer, endocrine therapy is an important treatment option. Tamoxifen (a selective estrogen receptor modulator [SERM]) has been the standard adjuvant endocrine treatment for postmenopausal women for decades. More recently, several clinical trials showed that the inclusion of an aromatase inhibitor (AI) in adjuvant endocrine therapy, for example, exemestane, anastrozole or letrozole improves survival relative to treatment with tamoxifen only.\textsuperscript{3}

Side effects of endocrine treatments

Endocrine treatments are aimed at estrogen deprivation by competitively binding to the estrogen receptor (ER), as is the case with the SERM tamoxifen or by interfering with estrogen biosynthesis, as is the case with AIs. Many side effects of endocrine therapy, such as hot flashes and mood disturbances, are related to estrogen deprivation and are common to both tamoxifen and AIs. In addition, tamoxifen has estrogenic effects that are beneficial in some tissues: tamoxifen lowers serum cholesterol levels and protects against bone loss and cardiovascular disease, but is also associated with a higher risk of endometrial cancer and thromboembolic disease.\textsuperscript{4} AIs are associated with a lower incidence of gynecological symptoms and hot flashes than tamoxifen. However, AIs are associated with musculoskeletal side effects, such as arthralgia, myalgia and bone loss.\textsuperscript{4}
Cognitive impairment as a known side effect of chemotherapy

Cognitive impairment, as reflected by memory and concentration problems, in cancer patients treated with chemotherapy for non-Central Nervous System (CNS) disease has received increasing attention in the last decade. The knowledge about this potential side effect of chemotherapy is growing, and current research aims to further increase the understanding of the incidence, severity, risk factors, and causes of cognitive dysfunction, as well as to improve ways to prevent or minimize adverse symptoms.

Rationale behind the study of potential cognitive side effects of endocrine treatment

Cognitive impairment as a potential side effect of endocrine treatments for breast cancer has not been well studied. The rationale for a study into potential effects of endocrine treatments on cognitive functioning can be found in the increasing evidence that estrogens are important for CNS functioning and cognitive functioning. There are many hypotheses related to estrogenic effects on brain tissue and brain functioning, including estrogenic activity through receptors that are present in brain structures important for cognitive functioning, such as the hippocampi and the cerebral cortex.

Evaluation of the putative neuroprotective effects of estrogens in neuropsychological studies in women has led to partial support for a beneficial influence of estrogens on cognitive functioning. For example, estrogen deprivation following surgical removal of the ovaries in premenopausal women is associated with decreased verbal memory performance, while estrogen replacement therapy (ERT) is associated with stable cognitive performance in women who have had ovariectomies. In addition, a case-control study suggests that long-term estrogen deprivation following surgical menopause increases the risk of dementia later in life. Harmful effects of estrogen on the brain, however, have also been described. In a large randomized, placebo-controlled trial, estrogen-containing hormone replacement therapy was associated with an increased risk of dementia and stroke in women over 65 years of age. This observation suggests that estrogens may only be neuroprotective during a critical time period around menopause and that estrogens offer no benefit to elderly women, in whom they may even have a detrimental effect.
Because of the association between estrogens and cognitive functioning, it is theoretically possible that endocrine therapy for breast cancer may also have an effect on cognitive functioning. Although endocrine therapy is widely used among breast cancer patients, the potential effects on cognitive functioning have hardly been studied.

Clinical importance of a study into potential cognitive side effects of endocrine treatment

Evaluation of potential cognitive effects of endocrine treatments for breast cancer is relevant because intact cognitive functioning is considered to be an important aspect of quality of life. The impact of a decrease in cognitive functioning on a patient’s quality of life might depend on, among others, the requirements of someone’s professional and social situation relative to her cognitive capacities. As a consequence, this impact might vary from woman to woman. Nevertheless, possible declines in cognitive functioning are a source of concern for many people. A specific study on the effects of endocrine treatments on cognitive functioning will improve the understanding of possibly distinctive, cognitive effects of different endocrine treatments. Furthermore, attention needs to be paid to the experiences of patients with respect to this important quality of life facet, as well as to the roles of other factors, such as anxiety/depression, fatigue, and endocrine treatment-specific side effects, in cognitive functioning. The derived knowledge can be used to provide patients and health care professionals with evidence-based information and guidelines regarding cognitive functioning. Such information has been scarce up to now. In the future, the derived knowledge may also be used for the development of intervention techniques for cancer patients who suffer from cognitive complaints and/or cognitive dysfunction.

Neuropsychological substudy of the TEAM trial

In 2001, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial started. The TEAM trial is an international, open-label, randomized study in postmenopausal hormone-sensitive breast cancer patients comparing the efficacy and safety of 5 years of adjuvant exemestane (25 mg/day) with 2.5 to 3 years of tamoxifen (20 mg/day) followed by 2 to 2.5 years of exemestane. This large international trial had national side studies regarding specific safety aspects, such as effects on bone health and blood lipids. The current thesis reports the results of the Dutch neuropsychological side study of the TEAM trial. This side study aimed to evaluate the effects of two endocrine treatments (the SERM
tamoxifen and the AI exemestane) on cognitive functioning in the context of a randomized design. Cognitive functioning was measured with a battery of neuropsychological tests, covering distinctive cognitive functions. The prospective character of the study and the inclusion of several self-reported measures of cognitive functioning and quality of life enabled us to investigate several additional relevant issues. Examples are the potential presence of cognitive dysfunction before the start of endocrine treatment and associations between self-reported cognitive functioning and cognitive test performance.

Outline of this thesis

Chapter 2 presents an overview of the current literature about possible influences of endocrine therapy for postmenopausal breast cancer on cognitive functions, such as memory, information processing speed and executive functioning. The first part of the review will provide an introduction to the influence of estrogens on cognitive functioning, with a focus on the effects detected in women during or after the menopausal transition. In the second part, the neuropsychological literature on the impact of endocrine therapy on cognitive functioning of breast cancer patients will be reviewed.

In Chapters 3 and 4, two studies with regard to cognitive functioning before the start of endocrine treatment are described. In the first study (Chapter 3) we examined the impact of four different definitions of cognitive impairment and two types of reference data (i.e., data from healthy postmenopausal women collected in the realm of the current study versus published normative data) on the prevalence of cognitive impairment. The second study (Chapter 4) aimed to indentify medical and psychological predictors for cognitive performance of breast cancer patients before the start of adjuvant treatment, and to compare cognitive performance of breast cancer patients and healthy controls, adjusted for medical and psychological variables.

Chapter 5 describes the core study of this thesis, a prospective study investigating the effects of tamoxifen and exemestane on cognitive functioning of postmenopausal breast cancer patients who had not received chemotherapy. Breast cancer patients participating in the TEAM trial underwent neuropsychological examinations before the start of tamoxifen or exemestane treatment, and after one year of continuous treatment. A healthy control group consisting of friends and relatives of the patients underwent the same tests twice with an interval of one year. One of the advantages of including a control
group is the possibility to account for practice effects which are inherent to repeated neuropsychological testing. Because of the prospective nature of the study, we were able to adjust for the cognitive differences between the groups at the first cognitive assessment.

Chapter 6 describes a cross-sectional study investigating neuropsychological functioning in postmenopausal breast cancer patients receiving endocrine treatment after completion of chemotherapy. Participants were breast cancer patients, included in the TEAM trial, who were randomly allocated to tamoxifen or exemestane after completion of doxorubicin/cyclophosphamide (AC) chemotherapy. They underwent neuropsychological examinations on average 2 years after continuous tamoxifen or exemestane treatment. The study aimed to compare cognitive functioning of AC/tamoxifen users with that of AC/exemestane users, and to compare cognitive functioning of the combined patient group with that of healthy control women.

The study described in Chapter 7 focused on self-reported cognitive functioning of breast cancer patients who used tamoxifen or exemestane. The prevalence of cognitive complaints and the self-reported frequency of cognitive failures, as well as associations between self-reported cognitive functioning, cognitive test performance, anxiety/depression, fatigue and menopausal complaints were evaluated.

The general discussion, Chapter 8, presents the aims and main conclusions of the studies. In addition, several methodological issues that have arisen from the studies will be discussed. The chapter concludes with issues regarding the interpretation of the findings, implications for clinical practice and recommendations for future research.
Reference List


Chapter 2

The influence of endocrine treatment for postmenopausal breast cancer on cognitive functioning: a review of the literature

Updated and adapted from:

Introduction

Endocrine treatment is an important option for patients with hormone-sensitive breast cancer. For decades, tamoxifen (a selective estrogen receptor modulator [SERM]) was the standard adjuvant endocrine treatment for postmenopausal women. Recently, several clinical trials showed that including an aromatase inhibitor (AI) in adjuvant endocrine therapy, for example anastrozole, letrozole or exemestane, further improves survival relative to treatment with tamoxifen only.\(^1\) Although generally well tolerated, endocrine treatments have side effects which are of clinical concern.\(^2\) Many side effects of endocrine therapy, such as hot flashes and mood disturbances, are related to estrogen deprivation and are common to tamoxifen and AIs. In addition, tamoxifen has estrogenic effects that are beneficial in some tissues: tamoxifen lowers serum cholesterol levels and protects against bone loss and cardiovascular disease, but is also associated with a higher risk of endometrial cancer and thromboembolic disease.\(^3\) AIs are associated with a lower incidence of gynecological symptoms and hot flashes than tamoxifen. However, AIs are associated with musculoskeletal side effects, such as arthralgia, myalgia and bone loss.\(^3\)

Whether the various endocrine treatments affect cognitive functioning has never been thoroughly studied and thus is largely unknown. Currently, the understanding of the role of estrogens in the brain and with respect to cognitive functioning grows. As a consequence, there are increasing concerns about the possible effects of endocrine treatments for breast cancer on cognitive functioning.\(^4\)

This chapter presents an overview of the current literature about possible influences of endocrine therapy for postmenopausal breast cancer on cognitive functions, such as memory, information processing speed and executive functioning. The first part of this review will provide an introduction into the influence of estrogens on cognitive functioning, with a focus on the effects found in women during and after the menopausal transition. In the second part, the neuropsychological literature on the impact of endocrine therapy for postmenopausal breast cancer patients on cognitive functioning will be reviewed.
The influence of estrogens on cognitive functioning

Evidence from basic neuroscience

The influence of estrogens on the female body is not restricted to the reproductive functions, but extends towards many physiological processes, such as processes that are important for bone density and cardiovascular functions. In addition, there is increasing evidence that estrogens play a role in central nervous system functioning. Preclinical neuroscientific studies indicate that estrogens exert neurotrophic and neuroprotective actions in the brain. The mechanisms of action of estrogens on brain structures are not entirely understood, however. There are many hypotheses for estrogenic actions on brain tissue and brain functioning, including estrogenic activity through receptors that are present in brain structures important for cognitive function, for example the hippocampi and the cerebral cortex. Furthermore, it has been suggested that estrogens have a beneficial effect on neurotransmitters that are involved in cognitive processes, such as the enhancement of cholinergic function. Other proposed beneficial effects are protection of the brain against ischemic damage by exerting anti-inflammatory actions after ischemic injury, promoting survival of brain cells and increasing cerebral blood flow and glucose transport into the brain.

Although up till now most of the research into the mechanisms of action of estrogens is not specifically aimed at the ‘aging’ brain, knowledge from basic neuroscience may be important to understand cognitive functioning in women during and after the menopausal transition.

Evidence from neuropsychological research in aging women

There is increasing evidence to suggest that normal aging is associated with cognitive decline in several cognitive domains, including memory, information processing speed and reasoning. In contrast, other cognitive functions, such as vocabulary and other aspects of intelligence are relatively stable and show only minor decline with aging. Given the link between estrogens and cognitive functioning established in basic neuroscience, as well as the fact that the ovarian production of estrogens decreases substantially in midlife, investigators have attempted to determine the influence of the decreasing estrogen levels, as well as the administration of estrogen to women following menopause, on cognitive functioning.
During the menopausal transition, levels of estrogen decrease gradually but substantially. Information about the influence of the natural menopausal transition on cognitive functioning is relatively scant. In general, no effects on cognitive functioning\(^{15-18}\) or, at the most, weak effects on particular cognitive domains, i.e. memory\(^ {19}\), information processing speed\(^ {20,21}\) or verbal fluency\(^ {22}\) are found.

In contrast with the gradual decline of estrogen levels in natural menopause, surgical menopause results in an abrupt drop of estrogen levels. Up till now, there are a few studies conducted into the influence of surgical menopause on cognitive functioning.\(^ {23-26}\) All these studies point in the same direction suggesting that surgical removal of the ovaries has an effect on verbal memory functioning coincident with the changes in plasma estrogen levels. Whether this is a transitory or lasting effect is not yet clear. A recent case-control study suggested that long-term estrogen deprivation following surgical menopause has long lasting effect as it is found to increase the risk of dementia occurring later in life.\(^ {27}\)

After the menopausal transition, estrogen levels are low, but in that low range individual hormone levels vary between women. Some authors have investigated associations between estrogen levels and cognitive performance in postmenopausal women, but the results of these studies are inconclusive. Some studies suggest that higher endogenous estrogen levels are related to better scores on verbal memory tasks\(^ {28-30}\), or to a smaller risk of cognitive decline.\(^ {31}\) Other studies\(^ {32,33}\) suggest the opposite effect, i.e. a detrimental effect of higher endogenous estrogen levels on memory and verbal fluency, respectively. Finally, some studies indentified mixed associations, depending on the evaluated cognitive domain\(^ {28}\), or no clinically meaningful association between serum estrogens and cognitive ability.\(^ {34}\)

In the last decades, numerous studies have evaluated the possible influences of hormone replacement therapy (HRT, mostly prescribed for relieving menopausal symptoms) on cognitive functioning and the risk of developing dementia. Although not all studies have provided support for a beneficial effect of the administration of estrogen on cognitive functioning, several meta-analyses showed a significantly reduced risk for developing dementia and Alzheimer’s disease in HRT users.\(^ {35-37}\)
In a large randomized, placebo-controlled study, the Women’s Health Initiative Memory Study (WHIMS), the effects of estrogen with or without a progestin on probable dementia and, secondarily, mild cognitive impairment were examined in healthy women over 65 years of age. Contrary to the expectations, a significantly increased risk of ‘probable dementia’ was found in the estrogen plus progestin group, the ‘estrogen alone’ group showed a non-significant increase in probable dementia. Remarkably, the risk of mild cognitive impairment, thought to be a precursor to Alzheimer’s disease, was not increased in both groups.\textsuperscript{38-41} In an attempt to resolve the inconsistencies in the literature regarding estrogen and cognition, the ‘critical-period’ hypothesis was formulated. According to this hypothesis, HRT optimally protects against cognitive decline when treatment is started close in time to menopause, whereas starting treatment decades afterwards is not beneficial or might even harm.\textsuperscript{13}

Possible explanations for the ‘critical period’ are for example that the rather rapid deprivation of estrogen at the time of menopause may have a more pronounced effect on neurons. HRT could conceivably prevent that detrimental effect. It is also possible that, after a long period of deprivation of estrogen, neurons become less sensitive to estrogen, or that older neurons have reduced responsibility for that hormone.\textsuperscript{42} Several reviews\textsuperscript{43,44} give support for the idea of a limited time window as they showed a beneficial effect of estrogen supplementation on certain cognitive functions (verbal memory and attention) in women under 65 years of age, but no effect in older women. However, there are also studies that do not support such a ‘critical period’ hypothesis.\textsuperscript{45}

**The influence of endocrine therapy for breast cancer on cognitive functioning**

In the etiology of breast cancer, estrogens play a major role. A high percentage of the malignant breast tumors depend on estrogens for their growth. In order to stop or slow down the growth of the tumor, endocrine therapy for postmenopausal breast cancer interferes with estrogen biosynthesis (AIs) or with the growth-promoting activity of estrogen (SERMs).

Because of the link between estrogens and cognitive functioning, it is theoretical plausible that endocrine therapy for breast cancer may have an effect on cognitive function. Although endocrine therapy is widely used among breast cancer patients, and often for many years, the potential effects on cognitive functioning are hardly studied.
This section will give an overview of the studies conducted up till now on the possible effects of endocrine therapy (AIs and SERMs, respectively) on cognitive function. PubMed was used to identify the studies. We used the search terms (‘Serm’ OR ‘tamoxifen’ OR ‘raloxifene’ OR ‘aromatase inhibitor’) AND (‘cognitive’ OR ‘memory’). We used the limits ‘human’ and ‘female’. Of the identified studies, we selected only studies that included neuropsychological measures. Some of these studies used additional neuro-imaging techniques or self-report measures to evaluate the effects of endocrine treatments on the brain. In this overview only the results of the neuropsychological measures are reported. All reported studies are, in chronological order, summarized in table 1.

Selective estrogen receptor modulators

In breast cancer treatment, tamoxifen is widely used in both pre- and postmenopausal patients. In the 1960’s, when the drug was synthesized, it was demonstrated to have anti-proliferating effects in the breast. The drug appeared to be capable of binding to the estrogen receptors in breast tissue, thereby preventing estrogen from promoting tumor growth. Tamoxifen thus became widely known as an anti-estrogen. Since then, it has been discovered that it, paradoxically, has many estrogenic qualities, including agonist effects on bone, blood lipids, and the endometrium. This finding led to the development of new drugs with specific and selective effects on the estrogen receptor function. Currently, tamoxifen and related drugs are collectively known as selective estrogen receptor modulators (SERMs).

Data on the impact of tamoxifen on cognitive function are scarce. The finding that tamoxifen treatment often induces hot flashes led to the hypothesis that tamoxifen acts as an estrogen antagonist within the central nervous system and may in the long term lead to cognitive deficits. Experimental evidence for a detrimental effect on memory was found in two experiments with mice. The results suggest that tamoxifen impairs memory function (particularly the retrieval of spatial information) in mice.

Six neuropsychological studies included tamoxifen users. Paganini-Hill and Clark were the first to investigate the effect of tamoxifen on cognitive functioning in breast cancer patients, using a questionnaire including three neuropsychological tests (clock drawing, copying a cube and narrative writing). Data from past tamoxifen users, current tamoxifen users and those who had never taken tamoxifen were analyzed. Using a cross-sectional
design, few differences were found between test scores of women who had used tamoxifen for the standard 5 years and those who had never taken it. Current users had significantly lower mean complexity scores on the narrative writing task. This study suggests that current use of tamoxifen may adversely affect cognition.

Ernst et al.\textsuperscript{47} and Eberling et al.\textsuperscript{51} used several neuropsychological tests in addition to neuro-imaging techniques (a screening instrument and tests for psychomotor speed\textsuperscript{47}, object naming, attention span, verbal memory, and pattern recognition\textsuperscript{51}) in small groups of breast cancer patients, estrogen users and control women. Only on the naming test a difference was observed between the groups: the tamoxifen users showed significantly poorer performance than estrogen users and healthy controls.

In one study, cognitive tests were administered in postmenopausal breast cancer patients who were randomized to tamoxifen, anastrozole (an AI) or the combination of both agents.\textsuperscript{52} Patients receiving endocrine therapy demonstrated impaired verbal memory and information processing speed compared with a healthy control group. Unfortunately, the authors did not distinguish between the three treatment arms, leaving unclear whether different endocrine agents have distinguishable effects on cognitive functioning.

In two small studies, the results indicated more severe cognitive impairment in anastrozole users compared to tamoxifen users. The first study showed that anastrozole users had significantly more severe impairment than tamoxifen users on tests for visual and verbal learning and memory.\textsuperscript{53} The second study\textsuperscript{54} included a healthy control group besides tamoxifen and anastrozole users. Both the patients taking tamoxifen as those taking anastrozole were more likely than healthy controls to show reliable cognitive decline from the start of treatment to 5-6 months later (39%, 64% and 7% respectively).

Although data on tamoxifen are sparse, the cognitive effects of another SERM (raloxifene) are well documented. Raloxifene differs from tamoxifen in the profile of estrogenic and anti-estrogenic qualities: it has anti-estrogenic qualities for both breast- as endometrial tissue, and estrogenic qualities for bone tissue. The role of raloxifene in the treatment of breast cancer is limited. According to the 2009 American Society of Clinical Oncology guideline on pharmacologic interventions for breast cancer risk reduction, raloxifene (60 mg/d) for 5 years may be offered as an option to reduce the risk of ER-positive invasive
breast cancer for postmenopausal women at increased risk for breast cancer. Raloxifene is currently primarily used in treatment and prevention of osteoporosis and therefore, most studies into the effects of raloxifene on cognitive functioning are conducted with patients with osteoporosis. Two large randomized placebo-controlled studies of postmenopausal women reported no significant detrimental effects of raloxifene on cognitive performance. Moreover, raloxifene in a dose 120 mg/day (but not 60 mg/day) resulted in a reduced risk of cognitive impairment.

From the studies described above, one might conclude that the effects of tamoxifen and raloxifene are opposite: detrimental effects of tamoxifen, but probable beneficial effects of raloxifene on cognitive functioning. However, a recent large prospective study among healthy postmenopausal women at increased risk for breast cancer, in which participants were randomly allocated to tamoxifen or raloxifene, showed no differences in cognitive functioning between tamoxifen and raloxifene users.

Aromatase inhibitors
Data on the effect of AIs on cognitive function are limited. AIs such as anastrozole, letrozole and exemestane almost completely inhibit the action of the enzyme aromatase, which is required for the peripheral conversion of testosterone and androstenedione to estrogen (the final step in the estrogen biosynthesis pathway). Consequently, aromatase inhibitors lower the level of circulating estrogen by almost 100%. To date, the only AI which effects on cognitive functioning have been investigated is anastrozole. Besides the three studies mentioned above that suggested more serious cognitive impairment in anastrozole users compared to tamoxifen users, one prospective study was conducted in anastrozole users. In this study, in which women at increased risk for breast cancer were randomized between anastrozole treatment and placebo, little or no cognitive impairment was found in anastrozole users after six months and two years. For the AIs letrozole and exemestane, no cognitive data are available yet.
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<td>Nickelsen et al. (1999)</td>
<td>Prospective design</td>
<td>143 women with osteoporosis (mean age 68 years); 3 groups: - RAL-users 60 mg (n=48; mean age 69.9 years) - RAL-users 120 mg (n=47; mean age 67.2 years) - PL group (n=48; mean age 68.2 years)</td>
<td>Memory Assessment Clinics battery Walter reed performance battery Geriatric depression scale</td>
<td>RAL did not impair cognitive functioning and did not affect mood in postmenopausal women treated for 1 year.</td>
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<td>Paganini-Hill &amp; Clark (2000)</td>
<td>Cross-sectional design</td>
<td>Breast cancer patients - past TAM users (short term: &lt;4 yrs; standard term: 4-5 yrs; long term: 6+yrs) (N=428; mean age 69 years) - current TAM users (short term: &lt;4 yrs; standard term: 4-5 yrs; long term: 6+yrs) (N=241; mean age 68 years) - never users (n=453; mean age 69 years)</td>
<td>Clock drawing task Copying a box drawing Narrative writing to describe a pictured scene. Geriatric Depression Scale Questions about memory problems</td>
<td>Little differences between test scores of women who had used TAM for the standard 5 years and never users. More women who had used TAM for ≥5 years reported seeing a physician for memory problems than non-users. Current users had significantly lower mean complexity score on the narrative writing task.</td>
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<tr>
<td>Yaffe et al. (2001)</td>
<td>Prospective design</td>
<td>7705 women with osteoporosis, (mean age 66 years). 3 groups: - RAL-users 60 mg (n=2481) - RAL-users 120 mg (n=2498) - PL group (n=2499)</td>
<td>Short blessed test Trailmaking A&amp;B Word list memory Word list fluency</td>
<td>RAL treatment for 3 years did not affect overall cognitive scores in postmenopausal women.</td>
</tr>
<tr>
<td>Ernst et al. (2002)</td>
<td>Cross-sectional design</td>
<td>Three groups of age-matched women: - breast cancer patients treated with TAM (n=16; mean age 70.4 years) - healthy women using HRT (n=27; mean age 71.5 years) - healthy CONs (n=33; mean age 71.8 years)</td>
<td>Modified MMSE Digit Symbol substitution test Trailmaking A</td>
<td>No differences in scores on cognitive tests.</td>
</tr>
<tr>
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<td>Jenkins <em>et al.</em> (2004)</td>
<td>Cross-sectional design Group comparisons Correlational analyses between cognitive measures and depression measures, and between length of treatment and cognitive performance</td>
<td>Breast cancer patients from the ATAC-trial: 1. Patient group (n=94; mean age 63.1 years) consisting of three subgroups: - TAM - ANA - ANA + TAM  2. Healthy CON group (n=35; mean age 60.9 years)</td>
<td>National adult reading test Wechsler Memory Scale: - paragraph recall, spatial span, digit span, letter-number sequencing, faces Kendrick digit copying task Broadbent Cognitive Failures Questionnaire (25 items) Beck depression inventory General Health Questionnaire</td>
<td>The patient group did not differ from the CON group on measures of working memory, attention and visual memory, but was significantly impaired on measures of verbal memory and processing speed.</td>
</tr>
<tr>
<td>Eberling <em>et al.</em> (2004)</td>
<td>Cross-sectional design Cognitive scores: comparison of group means.</td>
<td>40 postmenopausal women, 3 groups: - breast cancer patients using TAM (N=10; mean age 64.7 years) - women taking unopposed E (N=15; mean age 67.3 years) - women not taking TAM or E (N=15; mean age 66.5 years)</td>
<td>- Mini Mental State Examination - Verbal episodic memory - Semantic memory (object naming) - Verbal attention span - Pattern recognition Center for Epidemiologic Studies – Depression Scale</td>
<td>TAM users had significantly poorer scores on a semantic memory test than the other groups.</td>
</tr>
<tr>
<td>Yaffe <em>et al.</em> (2005)</td>
<td>Patients out of the Yaffe et al 2001 study that scored in the lowest 10th percentile on cognitive screening, or had clinical signs of dementia, were evaluated by a blinded dementia specialist to evaluate dementia etiology.</td>
<td>5386 women underwent cognitive screening (mean age 66 years). 3 groups: - RAL-users 60 mg (n=1792) - RAL-users 120 mg (n=1828) - PL group (n=1766). 744 women had evaluations for dementia etiology</td>
<td>Short blessed test Evaluation by a dementia specialist Brain scans Laboratory tests</td>
<td>3.4% of all women had mild cognitive impairment and 1% had dementia. RAL at a dose of 120 mg/day, but not 60 mg/day, resulted in reduced risk of cognitive impairment in postmenopausal women.</td>
</tr>
</tbody>
</table>
**Table 1 (continued).** Overview of studies on the effects of endocrine treatments for postmenopausal women on cognitive functioning

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>Participants</th>
<th>Measures</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bender et al. (2007)</strong>&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Cross-sectional design</td>
<td>Breast cancer patients, 2 groups:</td>
<td>Digit span, Digit vigilance test, Trailmaking A&amp;B, Rey Auditory verbal learning test, Rivermead Behavioral Memory Test, Rey Complex figure, Grooved Pegboard, National Adult Reading Test. Beck Depression Inventory, Profile of Mood States</td>
<td>Women on ANA had significantly more severe impairment than women on TAM on tests for: - visual learning and memory - verbal learning and memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- TAM users (n=16; mean age 48.2 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ANA users (n=15; mean age 57.4 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Jenkins et al. (2008)</strong>&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Prospective design; Measurements before the start of treatment and at 6 months and 24 months</td>
<td>Women at high risk for breast cancer, randomized between:</td>
<td>Auditory verbal learning test, Logical Memory, Complex Figure, Letter-number cancellation, Letter-number sequencing, Spatial span, Digit span, Stroop, Verbal fluency Broadbent Cognitive failures questionnaire General Health questionnaire FACT-B Endocrine subscale</td>
<td>Anastrozole use was not associated with cognitive impairment compared with placebo</td>
</tr>
</tbody>
</table>
Table 1 (continued). Overview of studies on the effects of endocrine treatments for postmenopausal women on cognitive functioning

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>Participants</th>
<th>Measures</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Collins et al. (2009) | Prospective design; measurements around the time of commencement of treatment (T1) and 5-6 months later (T2) Analysis of individual deviation scores | 3 groups:  
- TAM users (n=31; mean age 57.5 years)  
- ANA users (n=14; mean age 57.9 years)  
- Healthy CONs (n=28; mean age 59.3 years) | 18 neuropsychological tests:  
- Wechsler Adult Intelligence Scale-III: Symbol search, Letter-number sequencing, Digit-symbol coding, Digit span, Arithmetic, Block design.  
- Wechsler Memory Scale-III: Logical Memory II, Family pictures, Spatial span. Paced Auditory Serial Addition Task, Trailmaking A&B, Wisconsin Card Sorting Test, Controlled Oral Word Association Test, Grooved pegboard, California Verbal Learning Test, Rey Visual Learning Test, Consonant Trigrams, Boston Naming Test. Profile of Mood States | Both the patients taking tamoxifen and those taking anastrozole were more likely than healthy controls to show reliable cognitive decline from T1 to T2 (39, 64 and 7% respectively). |

Legault et al. (2009) Prospective design Measurements before the start of treatment and at 12 months and 24 months  
Women at high risk for breast cancer, randomized between:  
- tamoxifen (n=733; mean age 70.1 years)  
- raloxifene (n=765; mean age 69.7 years)  
Primary Mental Abilities-Vocabulary, Benton Visual Retention Test, California Verbal Learning Test, Verbal Fluency, Digit span, Finger tapping, Card rotations Positive and Negative Affect Schedule. Geriatric Depression Scale | Tamoxifen and raloxifene are associated with similar patterns of cognitive function in postmenopausal women at increased risk of breast cancer |

RAL = raloxifen; PL = placebo; TAM = tamoxifen; HRT = Hormone replacement therapy; CON = controle; ANA = anastrozole.
Problems regarding the interpretation of the findings of previous research

*Different classes of endocrine treatment and different agents in each class*

The main classes of endocrine treatment for postmenopausal breast cancer patients are SERMs and AIs. Given their different mechanisms of action, differences in the effects on cognitive functioning might be possible. SERMs may differ in their profile of estrogenic and anti-estrogenic properties, and consequently, in their effects on cognitive functioning. The current AIs differ with regard to androgenic properties: exemestane and its metabolites have weak androgenic properties whereas anastrozole and letrozole lack these properties. As it is known that androgens might provide benefits on performance in several cognitive domains, differences in cognitive effects between the three AIs might be possible.

*Role of age*

Studies on the effects of estrogens on cognitive functioning suggest that age might play an important role with respect to the effects of estrogen on cognition. The ‘critical-period-hypothesis’, holds that estrogen protects against cognitive decline when applied close in time to menopause, whereas estrogen administration decades afterwards is not beneficial or might even harm. With respect to the effects of endocrine treatment for breast cancer on cognitive functioning, there also might be different effects between patients who are close to the menopausal transition, and those whose menopausal transition took place many years ago. Until now, no study took the role of age into account.

*Cross-sectional versus prospective studies*

A considerable proportion of the studies had a cross-sectional design with one measurement during endocrine treatment. When a cross-sectional design is used, it is not possible to take into account potential cognitive differences between study groups that are already present before the start of endocrine treatment. Furthermore, the results of cross-sectional studies do not reflect cognitive changes over time associated with a particular treatment. However, prospective studies contend with other methodological problems. For example, neuropsychological test scores tend to improve with repeated testing despite the absence of underlying change in cognitive functioning. The optimal way to analyze prospective neuropsychological data has yet to be determined.
Participants: breast cancer patients versus healthy women at high risk for breast cancer
The participants of the reviewed studies were not in all cases breast cancer patients because the endocrine agents are not only used for the treatment of breast cancer, but also for breast cancer prevention, and in the case of raloxifene, for prevention and treatment of osteoporosis. It is possible that the effects of these agents on cognitive functioning are to some extent dependent on properties of the patient group. For example, breast cancer patients differ from healthy women with a high risk for breast cancer with regard to the diagnosis of cancer and previous treatments; and patients with osteoporosis might differ from breast cancer patients in their hormonal history, as osteoporosis is associated with lower levels of estrogens whereas breast cancer is associated with higher levels of estrogen.

Selection of neuropsychological tests and cognitive domains
In the studies conducted until now, a large diversity of neuropsychological tests is used. Some studies applied very limited testing\textsuperscript{52-54,62} while others used extensive batteries of tests covering multiple cognitive domains.\textsuperscript{65} There is some evidence that the influence of estrogen on cognitive functioning is restricted to several specific cognitive domains, such as verbal memory, information processing speed and aspects of executive functioning.\textsuperscript{57,59,62} An appropriate selection of test should include tests covering these domains. However, there is no consensus about the cognitive domains that are exclusively vulnerable to the effects of estrogen or endocrine treatment for breast cancer, indicating that batteries of tests should cover a wide range of cognitive domains.

Selection of control groups
The studies described in this review differ substantially with respect to the included control group. In some studies, a randomized design in which a control group using placebo was used.\textsuperscript{66} This is probably the optimal control group, but placebo-controlled designs are often not feasible when known effective therapy is available for the condition being studied.\textsuperscript{46,47,51,52,54} Other studies used healthy controls or a group of breast cancer patients who were not scheduled to receive the treatment under study.\textsuperscript{67} These control groups may be systematically different with respect to important sociodemographic and medical variables, which could influence cognitive outcomes. It is important to take into account these differences or control for them statistically.
Assessment of self-reported cognitive functioning and associations with cognitive test performance

One of the ways to get more insight in the clinical relevance of cognitive impairment found with cognitive tests is to ask patients to judge their cognitive functioning, for example by asking questions about cognitive complaints, experienced cognitive decline or by using a checklist with common failures of memory and concentration. However, a remarkable observation in neuropsychological research is that associations between self-reported cognitive functioning and cognitive test performance are weak. Although in the literature many potential explanations for the absence of clear associations are postulated, more insight in the nature and predictors of self-reported cognitive complaints is needed. In only three studies, a measure for self-reported cognitive functioning was used. However, no associations between those self-report measures and cognitive test performance were investigated in these studies.

Summary and conclusions

A considerable proportion of breast cancer patients are eligible for some kind of endocrine therapy. Although the nature of the possible effects of estrogens on cognitive functioning is becoming clearer, the potential cognitive effects of endocrine therapies for breast cancer have only been evaluated to a limited extent. Studies evaluating tamoxifen suggest that it has detrimental effects on cognitive functioning, while such effects are not found in studies evaluating raloxifene. Studies on anastrozole report more conflicting results with regard to its effect on cognition.

Many studies in the field of the impact of endocrine therapies on cognitive functioning are hampered by methodological shortcomings, such as large differences in selected cognitive measures between the studies, lack of data on anxiety/depression and fatigue to study their moderating effects in the relationships between endocrine therapy and cognitive functioning and absence of a baseline measurement.

In addition, most studies did not include self-report measures with regard to cognitive functioning. As a consequence, the question remains as to what extent the neuropsychological test scores actually reflect cognitive problems in daily life that patients have to deal with.
The role of endocrine therapy in breast cancer treatment is increasing, and the medical grounds for prescribing are expanding. As a consequence, increasing numbers of, often elderly, patients use endocrine therapy. Endocrine therapy often is used for several years and different agents can be used in succession. Because intact cognitive functioning is important for independent living and activities in daily life, it is important that the effects on cognition of the various endocrine agents and treatment regimens are included in long-term safety and quality of life studies. Large-scale longitudinal studies that use appropriate controls and that include measures of symptoms of depression, anxiety, psychosocial distress and fatigue are needed. Such studies should, among others, include verbal memory tasks, because this cognitive domain is probably most vulnerable to estrogenic effects. Furthermore, research that addresses mechanisms that might explain the results from neuropsychological studies is needed. Finally, an important issue that needs attention is the experience of the patients that use the various endocrine agents. After all, little is known about their cognitive complaints during therapy and the association with test scores and psychosocial features. Information from these studies can be used to make patients and clinicians aware of any cognitive side effects that have to be balanced against benefits of the endocrine treatments.

This thesis

This thesis describes a prospective study on the potential effects of two types of endocrine treatment (the SERM tamoxifen and the AI exemestane) on cognitive functioning in postmenopausal breast cancer patients. The patients were participants of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, an international, open label, randomized study comparing the efficacy and safety of 5 years of adjuvant exemestane (25 mg/day) with 2,5-3 years of tamoxifen (20 mg/day) followed by 2-2,5 years of exemestane.

The inclusion of a baseline measurement before the start of treatment enabled us to adjust for potential pre-treatment cognitive differences between study groups. In order to take into account practice effects, we added a healthy control group. We used a large, comprehensive battery of neuropsychological tests, as well as several measures for self-reported cognitive functioning, anxiety/depression, fatigue, and menopausal symptoms. The prospective nature of the study provided the opportunity to look in detail into cognitive functioning of breast cancer patients before the start of endocrine treatment. Methodological aspects were addressed, as well as a detailed evaluation of predictors for
cognitive functioning in breast cancer patients after surgery, but before the start of endocrine treatment. Because the TEAM trial also included breast cancer patients who received chemotherapy before the start of endocrine therapy, we had the opportunity to evaluate cognitive functioning in breast cancer patients who were exposed to both chemotherapy and endocrine treatment in an additional, cross-sectional study. Finally, associations between cognitive test performance, self-reported cognitive functioning, anxiety/depression, fatigue and menopausal symptoms were evaluated.
Chapter 2

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The influence of endocrine treatment on cognitive functioning: a review


Chapter 3

The impact of different definitions and reference groups on the prevalence of cognitive impairment: a study in postmenopausal breast cancer patients before the start of adjuvant systemic therapy


doi:10.1002/pon.1595
Abstract

Objective: Several prospective studies into the effects of adjuvant systemic therapy on cognitive functioning suggest that a proportion of breast cancer patients show cognitive deficits already before the start of systemic therapy. Due to, among others, methodological inconsistency, studies report different rates of this pre-treatment cognitive impairment. We examined the impact of four different criteria of cognitive impairment and two types of reference groups (a study-specific healthy reference group versus published normative data) on the prevalence of cognitive impairment.

Methods: Two-hundred and five postmenopausal breast cancer patients underwent a battery of neuropsychological tests before the start of endocrine therapy, 124 healthy subjects underwent the same tests. Proportions of cognitive impaired patients were calculated for each of four criteria for cognitive impairment, using (1) study-specific healthy controls and (2) published norms of healthy controls as reference groups.

Results: The prevalence of cognitive impairment varied greatly with the strictness of the criterion, as expected, but also was dependent on the reference group used. Cognitive impairment, relative to published norms, ranged from 1% for the strictest to 36.6% for the less strict criterion, cognitive impairment relative to study-specific healthy controls, ranged from 13.7% to 45.4% for the same criteria.

Conclusion: This study highlights contrasting proportions of cognitive impairment by using different criteria for cognitive impairment and different reference groups. (Dis)advantages of methods using a criterion for cognitive impairment, and of the use of published norms versus a study-specific reference group are discussed.
Introduction

The development of effective adjuvant chemo- and endocrine therapy led, besides the results of screening, to a substantially increased survival of breast cancer patients. Therefore, more attention is actually paid to the late side effects of treatments that affect quality of life in breast cancer survivors, such as cognitive impairment. In the past years, a growing number of studies documented the presence of cognitive impairment in a subgroup of cancer patients treated with adjuvant systemic therapy. As most studies were cross-sectional with cognitive assessments performed months to years after chemotherapy, it was impossible to analyze individual changes in cognitive performance over time or to control for baseline differences between groups. Therefore, the use of a prospective study design with a baseline assessment before the start of adjuvant systemic therapy is currently thought imperative.¹

One of the surprising findings in several prospective studies is that a subset of patients already shows cognitive deficits before the start of chemotherapy (see table 1 for an overview of the prospective studies which reported about cognitive functioning before the start of chemotherapy). The proportions of patients classified as ‘cognitively impaired’ at baseline vary from 11%² up to 35%.³ The finding of cognitive impairment before treatment emphasizes the need to study the mechanisms that could explain this phenomenon. In the literature several mechanisms have been proposed for pre-treatment cognitive dysfunction, for example impact of anxiety and depression on cognitive functioning (although these relationships appeared to be typically absent in studies so far)⁴ and negative effects of anesthesia and surgery undergone in the weeks before the baseline cognitive assessment.⁵ Specific disease-related factors, such as increased levels of proinflammatory cytokines have also been proposed as possible cause for cognitive impairment in cancer patients before treatment.⁶ Research in various neurodegenerative disorders, and in cancer patients receiving immunotherapy, has found associations between deregulation of cytokine activity and cognitive performance.⁷,⁸

Besides such subject-related matters, the extent to which pre-treatment cognitive impairment is observed might also be dependent on the methodology used to describe cognitive performance. For example, the results from analyses in which mean test scores of groups of patients/controls are compared can differ from analyses in which individual patients are classified as ‘cognitively impaired’ or ‘intact’ on the basis of a specific
definition. In the latter, different definitions for ‘cognitive impairment’ can lead to substantial differences in the observed prevalence of cognitive impairment. Furthermore, when a large number of tests are used, a particular definition could lead to a higher estimated prevalence of cognitive impairment than when the same definition is applied to a smaller battery of tests. Another potential source of variation in the observed prevalence of cognitive impairment is the chosen reference group, namely whether published normative data or a healthy reference group, composed for the particular study is used.

The methodological issues mentioned above are well known and generally accepted in the neuropsychological literature. In research into other neurocognitive states that are characterized by relatively mild cognitive problems, like ‘Mild Cognitive Impairment’, post-operative cognitive dysfunction and HIV-associated neurocognitive disorders, these issues also get attention. In cognitive studies in cancer patients these specific factors are often not considered explicitly. For example, often no clear rationale is given for the choice of a particular criterion for cognitive impairment or for the use of a particular reference group. Furthermore, the impact of the choice for a particular criterion or particular reference group on the results and interpretation of cognitive data remains frequently not discussed.

The focus of this study is on methodological issues of the assessment of cognitive performance in cancer patients. We aimed to investigate the impact of different definitions for cognitive impairment and different reference groups (published norms versus our own study-specific healthy control group) on the observed prevalence of cognitive impairment before the start of adjuvant systemic therapy in breast cancer patients. The results of a more in-depth subject-matter analysis of cognitive performance of breast cancer patients before the start of adjuvant systemic therapy will be reported separately.
Table 1. Methods used to determine cognitive dysfunction prior to adjuvant systemic treatment in breast cancer patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Compared to</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wefel et al., 2004</td>
<td>Published norms</td>
<td>A patient was classified as cognitively impaired if she had multiple test scores of &lt;-1.5 SD or 1 test score &lt;-2SD below the normative mean. Patients completed 5-14 tests</td>
<td>35% of the patients were classified as cognitively impaired</td>
</tr>
<tr>
<td>Cimprich et al., 2005</td>
<td>Published norms</td>
<td>Comparison of group mean scores with normative means</td>
<td>Mean test scores generally fell within the normal range for healthy adults</td>
</tr>
<tr>
<td>Fan et al., 2005</td>
<td>Non-specific healthy controls</td>
<td>For each of six subtests, an interpretive algorithm was applied to generate a result of normal, borderline, mild, moderate or severe impairment. An overall classification of neurocognitive dysfunction was determined using another algorithm</td>
<td>16% of the patients and 5% of the controls had moderate-severe cognitive dysfunction (p.=.02)</td>
</tr>
<tr>
<td>Schagen et al., 2006</td>
<td>Endocrine therapy controls</td>
<td>A patient was classified as cognitively impaired when she scored ≥2 SD’s below the mean of the healthy group on at least 3 of 24 test indices. This definition yields a ‘misclassification’ rate of 10% in the healthy control group</td>
<td>Before treatment: 12.8% of FEC pts, 21.4% of CTC pts, 29.8% of non-chemotherapy pts and 10% of healthy controls were classified as cognitively impaired (not statistically significant different)</td>
</tr>
<tr>
<td>Hurria et al., 2006</td>
<td>Published norms</td>
<td>A patient was classified as cognitively impaired when she score 2 SD’s below the published normative data on at least 2 out of 12 test indices</td>
<td>11% of patients were classified as cognitively impaired</td>
</tr>
<tr>
<td>Jenkins et al., 2006</td>
<td>Non-chemotherapy group + Study-specific healthy controls</td>
<td>Stepwise multiple regression using treatment group as a predictor, besides age, IQ, education, psychological distress and menopausal status</td>
<td>‘Treatment group’ did not significantly predict performance on any of 14 measures</td>
</tr>
<tr>
<td>Bender et al., 2006</td>
<td>Endocrine therapy controls</td>
<td>Comparison of group means</td>
<td>No statistically significant difference between groups</td>
</tr>
<tr>
<td>Hermelink et al., 2007</td>
<td>Published norms</td>
<td>Comparison of group means with normative means + individual classification (a patient was classified as cognitively impaired when she had ≥2 test scores (out of 12) in the lower 5% range</td>
<td>Group means were lower than normative means on 5 tests; 31% of the patients were classified as cognitively impaired</td>
</tr>
<tr>
<td>Ahles et al., 2008</td>
<td>Study-specific healthy controls</td>
<td>A patient was classified as having ‘lower than expected cognitive performance’ if she scored ≥1.5 SD below the mean of the control group on ≥3 out of 9 domains or ≥2 SD below the mean on ≥2 domains.</td>
<td>0% of stage 0 patients and 22% of stage 1-3 patients were classified as having ‘lower than expected cognitive performance’</td>
</tr>
<tr>
<td>Stewart et al., 2008</td>
<td>Endocrine therapy controls + published norms</td>
<td>Comparison of group mean scores with normative means</td>
<td>All mean test scores fell within the normal range relative to published norms</td>
</tr>
</tbody>
</table>

FEC = chemotherapy with 5-Fluorouracil, Epirubicin and Cyclophosphamide.  
CTC = high dose chemotherapy with Cyclophosphamide, Thiotepa and Carboplatin, with bone marrow rescue.
Method

Participants and enrollment procedure

In the context of a prospective study on the impact of endocrine therapy on cognitive functioning, we conducted neuropsychological assessments in postmenopausal breast cancer patients after surgery, but before the start of any adjuvant systemic therapy. A group of healthy females of approximately the same age underwent the same neuropsychological testing.

Patients were female breast cancer patients participating in the Tamoxifen and Exemestane Adjuvant Multinational trial (TEAM trial; an international, open label, randomized study). The TEAM trial compares the efficacy and safety of 5 years of adjuvant exemestane (an aromatase inhibitor) with 2.5 years of tamoxifen (a selective estrogen receptor modulator) followed by 2.5 years of exemestane in postmenopausal women with early hormone sensitive breast cancer. Full in- and exclusion criteria of the Dutch TEAM trial are described elsewhere. In short, patients had histologically/cytologically confirmed adenocarcinoma of the breast, had undergone surgery with a curative intent and had an estrogen receptor- and/or progesterone receptor-positive tumor. For this neuropsychological side study, only patients who were not scheduled to receive chemotherapy were eligible. Additional exclusion criteria were: Central Nervous System (CNS) disease, not being fluent in Dutch and signs of dementia according to a dementia screenings tool (7 minutes screen). A central medical ethics committee and the local medical ethic committees of all participating hospitals approved the neuropsychological study. Enrollment of patients took place between October 2003 and January 2006. Patients were approached by their clinicians; the researchers carried out the informed consent procedure. The neuropsychological assessments took approximately 2.5 hours to complete. For each participant the administration of tests and questionnaires took place in the same order. A healthy control group consisted of female friends or family members of approximately the same age of the participating TEAM patients. We chose a healthy control group to minimize sociodemographic differences between the patients and controls. Inclusion criteria for controls were: postmenopausal status, no history of malignant disease or CNS disease, fluent in the Dutch language and no signs of dementia according to a dementia screenings tool (7 minutes screen).
Assessment of neuropsychological performance

A comprehensive test battery was designed to assess a broad range of eight specific cognitive domains, comprising 18 test indices (see table 2). The choice for these eight domains was based on (1) earlier studies into the cognitive effects of chemotherapy which indicated that impairment was found in multiple cognitive domains and (2) literature-based hypotheses about the cognitive effects of estrogens. The results with respect to baseline performance on these cognitive domains will be reported separately.

Besides the 18 outcome-variables, the Dutch Adult Reading Test was used as a measure of pre-morbid verbal intelligence. Also, a dementia-screening tool was included to detect participants with signs of beginning dementia (7-minutes screen). The tests were selected for reliability, validity, availability of published normative data and suitability for older age groups. All tests are widely used in clinical neuropsychological practice and the psychometric properties are well described.

Data-analysis

The Statistical Package for Social Sciences (SPSS) Windows 15.0 was used for statistical analyses. In case neuropsychological test scores were missing (approximately 0.7% of the total number of test scores), estimates on the base of age and IQ were imputed using an expectation-maximization (EM) algorithm implemented in SPSS. Patients and controls were then divided into ‘cognitively intact’ versus ‘cognitively impaired’ groups. In order to do so, we defined failure on an individual test as a score at least 2 SD’s below the mean using (1) healthy controls and (2) published norms as a reference. This cut-off point is chosen as it is generally considered meaningful in clinical neuropsychological practice. The distribution of cognitively impaired versus intact participants was described using four different, commonly used definitions, decreasing in strictness (failure on ≥4, ≥3, ≥2 and ≥1 test, respectively). For each definition and each reference group (published norms and our study-specific healthy control group), differences in proportions of cognitively impaired persons were tested by means of Chi\(^2\) and logistic regression analyses. A \(P\)-value less than 0.05 was required for significance.
### Table 2. Summary of cognitive test measures, outcome variables and origin of published norms

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Cognitive tests</th>
<th>Outcome variable</th>
<th>Score range</th>
<th>Origin of norms</th>
<th>Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal memory</strong></td>
<td>Rey auditory verbal learning test(^{25}) (Dutch shortened version)</td>
<td>1. Total of 3 trials</td>
<td>0-45</td>
<td>Data from a Dutch population-based study among 3107 participants aged 55-85 years(^{27}) Dutch patients (n=540; age 16-62 years) with various neurological ailments</td>
<td>Age, Sex, Education</td>
</tr>
<tr>
<td></td>
<td>Visual Association Test(^{26})</td>
<td>2. Total for long delay trial</td>
<td>0-15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Total of 2 trials</td>
<td>0-24</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visual memory</strong></td>
<td>Wechsler Memory Scale revised – visual memory(^{28}) 1. Immediate recall 2. Delayed recall</td>
<td>4. Points awarded according to scoring criteria</td>
<td>0-41</td>
<td>American normative data from WMS manual</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Points awarded according to scoring criteria</td>
<td>0-41</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td>WAIS III Letter-number sequencing(^{29})</td>
<td>6. Total correct trials</td>
<td>0-21</td>
<td>Normative data of the Dutch Version of the WAIS-III</td>
<td>Age</td>
</tr>
<tr>
<td><strong>Information processing speed</strong></td>
<td>Stroop Card 1(^{30})</td>
<td>7. Seconds to complete</td>
<td>0+</td>
<td>Stroop test: based on 585 persons aged 14-87 yrs from two population-based studies (n=330), healthy volunteers (n=65) and patients who appeared cognitive intact in clinical cognitive examination (n=190)</td>
<td>Age, Sex, Education</td>
</tr>
<tr>
<td></td>
<td>Stroop Card 2(^{30})</td>
<td>8. Seconds to complete</td>
<td>0+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trailmaking A(^{31})</td>
<td>9. Seconds to complete</td>
<td>0+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mental flexibility</strong></td>
<td>Stroop Card 3(^{30})</td>
<td>10. Seconds to complete</td>
<td>0+</td>
<td>Trailmaking test: based on 342 persons aged 17-87 yrs from a population-based study (n=78), healthy volunteers (n=66) and patients who appeared cognitive intact in clinical cognitive examination (n=198)</td>
<td>Age, Sex, Education</td>
</tr>
<tr>
<td></td>
<td>Trailmaking B(^{31})</td>
<td>11. Seconds to complete</td>
<td>0+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reaction times</strong></td>
<td>Fepsy Reaction times:(^{32}) 1. dominant hand 2. non-dominant hand</td>
<td>12. Mean msec/30 trials</td>
<td>0+</td>
<td>Normative data from FePsy (1995). Based on 27 healthy controls aged 31-65+.</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13. Mean msec/30 trials</td>
<td>0+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Manual motor speed</strong></td>
<td>Fepsy Finger tapping:(^{32}) 1. dominant hand 2. non-dominant hand</td>
<td>14. Mean score of 5 trials of 10 seconds</td>
<td>0+</td>
<td>American normative data from Trahan et al. (1987). Based on 35 females aged 48-62 and 19 females aged 63-91.</td>
<td>Age, Sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15. Mean score of 5 trials of 10 seconds</td>
<td>0+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal fluency</strong></td>
<td>Letter fluency (D,A,T)(^{31})</td>
<td>16. Total score of 3 letters/1 minute each</td>
<td>0+</td>
<td>Based on 200 healthy volunteers aged 17-89 years.</td>
<td>NART-IQ</td>
</tr>
<tr>
<td></td>
<td>Category Fluency (Animals/professions)(^{34})</td>
<td>17. Total score 1 minute</td>
<td>0+</td>
<td>Normative data from a Dutch population-based study among 1856 healthy persons aged 24-81 years.</td>
<td>Age, Sex, Education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18. Total score 1 minute</td>
<td>0+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WAIS = Wechsler Adult Intelligence Scale; NART = National Adult Reading Test.
Results

Participant characteristics

Three hundred and thirty-one TEAM patients were eligible for the study in the period of enrollment. Eighty-five patients (26%) refused to participate because of lack of interest or too much burden, while 40 participants (12%) could not be included in the study, mainly due to logistic problems in the respective hospitals. Ultimately, 206 patients were tested (participation rate: 62%), whereby one patient was excluded from further analyses because of a score above the cut-off score of the dementia screenings test (7 minutes screen). The final study sample consisted of 205 patients. In the comparison group 124 healthy controls were included (none were excluded based on performance on the 7 minutes screen).

Table 3 shows the sociodemographic characteristics of the study sample. There were small, but statistically significant differences between the patient- and the control group for age, level of education and for estimated premorbid IQ. Therefore, subsequent analyses were, if appropriate, adjusted for age and IQ differences.

Table 3. Sociodemographic characteristics of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=205)</th>
<th>Controls (n=124)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (SD)</td>
<td>68.9 (7.4)</td>
<td>66.5 (8.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>range 50-84</td>
<td>range 49-87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>61.0 (125)</td>
<td>59.7 (74)</td>
<td>0.82</td>
</tr>
<tr>
<td>Single</td>
<td>39.0 (80)</td>
<td>40.3 (50)</td>
<td></td>
</tr>
<tr>
<td>Education, % (n) b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>32.7 (67)</td>
<td>17.7 (22)</td>
<td>0.005</td>
</tr>
<tr>
<td>Middle</td>
<td>48.3 (99)</td>
<td>52.4 (65)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19.0 (39)</td>
<td>29.8 (37)</td>
<td></td>
</tr>
<tr>
<td>Premorbid IQ (SD) c</td>
<td>99.8 (19.5) range 56-140</td>
<td>105.5 (19.0) range 59-140</td>
<td>0.009</td>
</tr>
</tbody>
</table>

a Single = Widowed, divorced, separated, never married.
b Low: primary school, Middle: secondary school, High: Graduate school/University.
c Estimated with the National Adult Reading Test.

Neuropsychological test norms

For all tests, we selected the most appropriate normative data that were available in the Netherlands (see table 2 for the origin of the normative data). Criteria for selection were: based on cognitive intact, Dutch speaking controls; recently published or made available,
taking into account sex, age and/or education or IQ, and providing data from an elderly age cohort. For most tests, normative data met these requirements.

Prevalence of “cognitive impairment” relative to different definitions and different normative standards

The proportions of patients classified as ‘cognitively impaired’ were, for all four definitions, substantially higher when we compared them with our study-specific control group than when we compared them with published normative data (see table 4), but none of the differences remained statistically significant after adjustment for age and IQ. The left part of table 4 shows, based on the scores of our own healthy controls, the proportions of patients and healthy controls classified as ‘cognitively impaired’ according to four different definitions, decreasing in strictness. As expected, the proportions ‘cognitively impaired’ patients and controls increased when the strictness of the definition decreased. When we determined the proportions of ‘cognitively impaired’ persons in the patient group and in our study-specific healthy control group on the base of published normative data (right part of table 4), we found that application of the two strictest definitions resulted in very low proportions of cognitively impaired persons in both the patient- and the control group (0.8% – 3.2%). Decreasing the strictness resulted, as expected, in higher proportions, but for none of the definitions statistically significant differences were observed between patients and healthy controls.

Table 4. Patients and controls classified as ‘cognitively impaired’ using different criteria and different normative standards

<table>
<thead>
<tr>
<th>No. of tests failed</th>
<th>Compared to our own control group</th>
<th>Compared to normative data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients % (n)</td>
<td>Own controls % (n)</td>
</tr>
<tr>
<td>≥4 tests failed</td>
<td>13.7 (28)</td>
<td>5.6 (7)</td>
</tr>
<tr>
<td>≥3 tests failed</td>
<td>17.6 (36)</td>
<td>8.1 (10)</td>
</tr>
<tr>
<td>≥2 tests failed</td>
<td>27.3 (56)</td>
<td>13.7 (17)</td>
</tr>
<tr>
<td>≥1 tests failed</td>
<td>45.4 (93)</td>
<td>33.1 (41)</td>
</tr>
</tbody>
</table>

*P: p-value of Chi² test; P*: p-value of logistic regression with covariates age and IQ.*
Discussion
The aim of this study was to demonstrate the impact of different definitions and different reference groups on the estimated prevalence of cognitive impairment before the start of adjuvant endocrine therapy in breast cancer patients. In cognitive studies with cancer patients many different definitions for cognitive impairment are used, often without a clear rationale. In addition, some studies made use of published norms \(^2,3,13,18,19\) while other studies included a study-specific healthy reference group.\(^7,14-17,19\) The impact of these methodological differences on the study results and interpretation is difficult to estimate and, as a consequence, the comparability of the studies is limited.

Our analyses showed that the prevalence of cognitive impairment varied greatly with the strictness of the definition, as expected (range from 13.7 % to 45.4% based on study-specific controls; range from 1% to 36.6% based on published norms). We also found that the estimated prevalence of cognitive impairment varied greatly as a function of the reference group used (study-specific healthy controls versus published data of healthy controls). For example, with cognitive impairment defined as failure on ≥2 tests, we found a prevalence of 27.3% when we used study-specific controls, versus 11.2% when we used published normative data.

With respect to definitions for cognitive impairment, a disadvantage of all methods using such definitions is that they are based on more or less arbitrary decisions, which can influence the results substantially. This applies for the cut-off point for failure on a single test and for the number of failed tests to classify a person as ‘cognitively impaired’. Another drawback of methods that use definitions is that continuous data from multiple tests is reduced to only two categories (‘cognitively unimpaired’ versus ‘cognitively impaired’). Categorizing continuous data leads to loss of information; therefore it might be more difficult to find small differences that have statistical and, potentially, clinical significance. The extent to which methods using definitions and methods comparing mean test scores between groups will produce different results depends on, among others, group sizes and the distribution of test scores within the groups.

With respect to reference groups, an advantage of the use of a study-specific reference group above published norms is the possibility to evaluate the impact of a particular criterion on the calculated prevalence of ‘cognitive impairment’ in the reference group.
and to compare the calculated proportions in patients and controls. This provides the possibility to prove the particular criterion. If only published norms are used, such a check is not possible, leaving uncertainty about the accurateness of the chosen criterion and, subsequently, the reported proportion of ‘cognitively impaired’ patients. Another advantage of a study-specific reference group above published norms is that the same tests are applied on both patients and controls. Published normative data of each test originate from different normative samples of possibly diverse quality, reducing the possibilities to combine different tests to, for example, cognitive domains or to compare different test results with each other. However, study-specific reference groups are not without problems too. For example, in study-specific reference groups consisting of family and friends (as in the current study), selection bias is easily introduced because patients might invite persons who they consider at ease with cognitive testing and/or have a higher mean IQ than the patients themselves. Additionally, it is often not easy to compose a study-specific reference group of a sufficient size. In such cases, normative data derived from a large age- and IQ stratified sample might be preferred above a small study-specific reference group.

Our data showed, in the comparison of the patients with our own controls, that the proportions of ‘cognitively impaired’ persons differ significantly before adjustment for age and IQ, but that these differences are not longer significant after adjustment for these covariates. This indicates that small differences in age and IQ between the groups have a substantial impact on the test results. Because age and IQ are well known predictors for cognitive performance and are probably even more prominent in older age groups, our data stress the importance of taking these covariates into account sufficiently. When a study-specific reference group is used, careful matching on these variables is important. When published norms are used, large normative samples in which elderly subgroups are represented sufficiently are imperative.

The strength of this study is that the size of both the patient- and the healthy control group is high compared to other study samples in this research field. A limitation of our study might be the suboptimal quality of the published norms for several tests that we used, possibly having biased the results. The development of normative data is an expensive and time-consuming matter that often has less priority than it deserves. This is especially a problem in small countries or small language areas, such as the Netherlands.
Although the quality of published norms is probably better in larger countries, shortcomings in the quality of the published normative data seem to be universal\textsuperscript{21} and can influence the results to a large extent. Another limitation is the non-perfect match with respect to age and IQ between our patients and healthy controls, making statistical adjustment for these differences necessary.

In conclusion, the estimated prevalence of cognitive impairment in a particular patient group is highly dependent on the used definition for cognitive impairment and the reference group to which patients are compared. As a consequence, the scope of the problem of cognitive impairment before the start of adjuvant systemic treatment for breast cancer is not yet sufficiently clear. In some studies conducted so far the prevalence of cognitive impairment is probably overestimated due to the use of a relatively ‘weak’ criterion combined with the lack of a study-specific reference group, as a result of which the criterion could not be proved.\textsuperscript{3,18}

Our data stress the need for consensus on the measures and statistical methods to study cognitive impairment both before as during/after adjuvant systemic therapy. Considering the methods used in neuropsychological studies in other patient groups that are characterized by mild cognitive impairment might be helpful in reaching this consensus. In order to find the best methods to evaluate cognitive impairment associated with cancer and cancer treatments, an international group of researchers started a Task Force in order to stimulate standardization and improvement of research methods.\textsuperscript{35}

Acknowledgements

We are indebted to all patients, healthy controls as well as physicians and research nurses of 38 Dutch hospitals that participated in this cognitive study. We are also grateful to the Datacenter Heelkunde of the Leiden University Medical Center for organizational support and to M. Weevers, S. Leering and A. van Nuland for helping collecting the data. This original work was supported by an independent research grant from Pfizer, grant number 56850.
Reference List


The impact of different definitions and reference groups on the prevalence of cognitive impairment


Cognitive functioning of postmenopausal breast cancer patients before adjuvant systemic therapy, and its association with medical and psychological factors

Christina M Schilder, Caroline Seynaeve, Sabine C Linn, Willem Boogerd, Louk V Beex, Chad M Gundy, Johan W Nortier, Cornelis J van de Velde, Frits S van Dam, Sanne B Schagen. Critical Reviews in Oncology/Hematology 2009; Dec. 23 [epub ahead of print]
doi: 10.1016/j.critrevonc.2009.11.001
Abstract

Purpose: This study aimed to identify medical and psychological predictors for cognitive performance of breast cancer (BC) patients before the start of adjuvant systemic treatment and to compare cognitive performance between BC patients and healthy controls adjusting for medical and psychological variables.

Material: 205 postmenopausal BC patients underwent pre-treatment neuropsychological tests and provided medical and psychological data. 124 healthy controls underwent the same assessment.

Results: ‘Treatment for diabetes mellitus’ and/or ‘hypertension’, ‘less hours spent on cognitively stimulating activities’, ‘fewer days since surgery’ and ‘more reproductive years’ were associated with worse cognitive performance in the BC patients, independent of age and IQ. Cognitive differences between BC patients and healthy controls could partly be explained by the evaluated variables.

Conclusion: The results stress the need for adjustment for pre-treatment cognitive differences between study groups, and also indicate that further research into pre-treatment cognitive dysfunction is warranted.
Introduction

The effects of adjuvant systemic therapy on cognitive functioning in breast cancer (BC) patients are increasingly studied. Many of the published studies showed cognitive deficits after the administration of chemotherapeutic drugs, at least in a subset of cancer patients.\(^1\) While early studies mainly were cross-sectional in nature, recent studies predominantly have a prospective design with a baseline measurement (i.e. before the start of adjuvant therapy). Most\(^2\) to \(^7\), but not all\(^8\) to \(^11\) of the latter studies showed that a subset of BC patients performed below expected levels already before the start of adjuvant therapy. Little is known about the possible explanations of this pre-treatment cognitive impairment that is reported in the majority of studies. Possible explanations postulated in the literature include methodological issues\(^12\), aspects of the biology of BC that influence cognitive functioning, as well as shared risk factors for the development of cancer and cognitive impairment, although empirical evidence for the latter explanations is lacking.\(^13\)

Alternative explanations for cognitive impairment before the start of adjuvant systemic treatment could be factors related either to BC treatment (e.g. lingering effects of surgery and anesthesia\(^14\), radiotherapy) and to fatigue, anxiety/distress or depression secondary to the diagnosis and treatment of BC.\(^1\) Further, factors associated with activities in daily life (such as frequency of physical\(^15\) and cognitively stimulating activities (e.g. reading, playing games, making puzzles)\(^16\), co-morbidities (for example diabetes mellitus\(^17\), hypertension\(^18\)), as well as estrogen exposure during lifetime\(^19\) might be involved in cognitive performance after BC diagnosis.

In order to increase the understanding of the occurrence of cognitive impairment prior to the start of systemic treatment, the aims of this study were twofold. The first aim was to identify, out of a range of relevant medical and psychological variables, predictors for cognitive performance in postmenopausal BC patients before the start of adjuvant systemic therapy. Secondly, we aimed to compare cognitive functioning of the BC patients with that of healthy controls, and determined the explanatory role of the evaluated factors.
Materials and methods

Participants and enrollment procedure

This study was conducted within the framework of a prospective study on the influence of two types of endocrine therapy (tamoxifen and exemestane) on cognitive functioning in postmenopausal BC patients. Dutch female BC patients participating in the Tamoxifen and Exemestane Adjuvant Multinational trial (TEAM trial; an international, open label, randomized study) were invited to take part in the neuropsychological side study. The TEAM trial compares the efficacy and safety of 5 years of adjuvant exemestane (aromatase inhibitor) with 2.5 years of tamoxifen (selective estrogen receptor modulator, SERM) followed by 2.5 years of exemestane in postmenopausal women with early, hormone-sensitive BC. Detailed in- and exclusion criteria of the TEAM trial are described elsewhere. In short, patients had histologically/cytologically confirmed adenocarcinoma of the breast, had undergone surgery with a curative intent and had an estrogen receptor- and/or progesterone receptor-positive tumor. For the neuropsychological side study additional exclusion criteria were: adjuvant chemotherapy, Central Nervous System (CNS) disease, not being fluent in Dutch and signs of dementia according to a dementia screenings tool (7 minutes screen).

A healthy control group consisted of friends or family members, invited by the participating TEAM patients, of approximately the same age. Inclusion criteria for controls were: postmenopausal status, no history of CNS disease or malignant disease, fluent in the Dutch language and no signs of dementia according to a dementia screenings tool (7 minutes screen). For this healthy control group, we aimed for a sample size of at least the sample size of the two separate patient groups (patients about to start with tamoxifen or exemestane). For the current study, we combined the tamoxifen and exemestane group into one patient group. Neuropsychological assessments in the BC patient group took place after surgery, but before the start of adjuvant systemic therapy.

Tests and questionnaires were administered in a fixed order. The neuropsychological assessments took approximately 2.5 hours to complete. The medical ethic committees of all participating hospitals in the Netherlands approved the neuropsychological study. All participants provided written informed consent.
Measures

Cognitive tests
A comprehensive test battery, existing of 18 test indices, was designed to assess a broad range of cognitive functions (see table 3). Based on literature data and our neuropsychological expertise all tests were classified in one of eight cognitive domains (verbal memory, visual memory, information processing speed, executive functioning, manual motor speed, reaction speed, wording memory and verbal fluency, see table 3). Additionally, the Dutch Adult Reading Test was used as an estimate for verbal intelligence. The tests were selected for reliability, validity, sensitivity for effects of hormones and suitability for older age groups.

Determination of covariates
Information on demographic, medical and psychological variables was collected from either the questionnaires or the medical files. In following paragraphs the items on which data were recorded are specified.

Age, IQ
Age and IQ are known strong predictors for cognitive test scores. IQ was estimated by means of the Dutch adult reading test (NART).

Comorbidity/medications
Patients and healthy controls were asked whether they were treated for diabetes mellitus or/and hypertension (yes/no). Data on the current use of benzodiazepines (yes/no) and/or anti-depressants (yes/no) were extracted from the self-reported list of prescription medications provided at baseline by all participants.

Indicators for lifetime estrogen exposure
As an indicator for the lifetime period of endogenous estrogen exposure we calculated the number of years between the (self reported) menarche and the end of regular menstrual cycles, and subtracted for each child 9 months of this period of time. This is indicated as “reproductive period”. Furthermore, we asked for (ever) use of Hormone Replacement Therapy (HRT) (yes/no).
Physical and cognitively stimulating activities before BC diagnosis

As measures for activities before BC diagnosis were taken: employment (yes/no); self reported mean number of hours daily spent on cognitively stimulating activities: reading and making (crossword) puzzles/games etc. (composite score of two 4-point items ranging from < 1 hour to > 4 hours), and quantity of physical activities: walking/cycling/sports activities and gardening (composite score of two 7-point scale items ranging from ‘hardly ever’ to ‘every day’). These measures are based on questionnaires that are used in a Dutch longitudinal aging study\textsuperscript{24} and by Statistics Netherlands (CBS; http://statline.cbs.nl).

Variables related to breast cancer treatment (patients only)

Days since definite surgery (lump- or mastectomy, or axillary dissection) for BC and ongoing radiotherapy (yes/no) were extracted from medical files. The physical functioning scale from the EORTC QLQ-C30 quality of life questionnaire was used as a measure for reported ongoing physical problems.\textsuperscript{25} This scale contains 5 items, each was rated on a 4-point scale ranging from ‘not at all’ to ‘very serious’.

Psychosocial measures

To measure the level of anxiety/depression at the baseline assessment, the 25-item Hopkins Symptom Checklist (HSCL) was used. Participants rated all items on a 4-point scale. A mean item score of ≥ 1.55 is considered as a cut-off point for a ‘possibly depressive case’.\textsuperscript{26} As a measure for fatigue, the fatigue subscale (containing 3 items rated on a 4-point scale) of the EORTC QLQ-C30 was used.\textsuperscript{25}

Data analyses

The Statistical Package for Social Sciences (SPSS) WINDOWS 15.0 was used for all analyses. In order to create cognitive domain scores out of separate test scores and to make results comparable, all raw (not age-adjusted) cognitive test scores were converted to standardized Z-scores based on the mean and standard deviation of the healthy control group. Eight cognitive domain scores were expressed as the mean Z-score of the tests that made up the particular cognitive domain (see table 3). Data from questionnaires were converted to scores according to standard scoring rules. Missing values (less than 1% of all scores on tests and questionnaires) were estimated with an expectation-maximization (EM) algorithm implemented in SPSS.
Differences in sociodemographic and medical characteristics between groups were analyzed by means of χ² tests for contingency tables or univariate analysis of variance (ANOVA). Differences between groups on scales from questionnaires were determined by ANOVA’s.

For the eight cognitive domains separately, hierarchical multiple regression was used to identify predictors for cognitive performance in the BC patient group. Age and IQ comprised the first step, as their associations with cognitive performance are undisputed, followed in the second step by all other variables (see table 1). Subsequently, variables that were identified as predictive for cognitive performance were entered in a final model for each cognitive domain. Because we evaluated the impact of 16 possible predictors, we used $P=0.01$ as criterion for entry instead of the conventional $P=0.05$.

The comparison of cognitive functioning between patients and healthy controls was conducted by means of MANCOVA across the eight cognitive domains and subsequent univariate ANCOVA’s. Analogously to the analyses in the patient group only, age and IQ, were entered as covariates. Secondly, to investigate the contribution of the significant predictors for cognitive performance in the patient group, these predictors were used as covariates in addition to age and IQ in a second MANCOVA. Thirdly, other potentially relevant covariates as described in the methods section (i.e. except the patient-exclusive variables ‘time since surgery’ and ‘ongoing radiotherapy’) were added to evaluate their additional explanatory value in cognitive differences between BC patients and healthy controls. Effects-sizes were calculated with Cohen’s $d$ and based on the partial eta-squared after adjustment for covariates. For all analyses, a two-sided $P$-value less than 0.05 was required for significance.

Results

Participant characteristics

During the period of enrollment, 331 TEAM patients were eligible for the study. Eighty-five patients (26%) refused to participate because of lack of interest or too much burden, while 40 participants (12%) could not be included in the study, mainly due to logistic problems in the respective hospitals. Ultimately, 206 patients underwent the baseline neuropsychological testing (participation rate: 62%). One patient was excluded from
further analyses because of a score above the cut-off score of the dementia screenings test (7 minutes screen). So, the final study sample consisted of 205 patients. In the comparison group 124 healthy controls were included (none were excluded based on performance on the 7 minutes screen).

Table 1. Sociodemographic, medical, treatment-related and psychological characteristics

<table>
<thead>
<tr>
<th></th>
<th>BC patients (n=205)</th>
<th>Healthy controls (n=124)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; yrs; mean (SD) range</td>
<td>68.9 (7.4) 50-84</td>
<td>66.5 (8.0) 49-87</td>
<td>0.006</td>
</tr>
<tr>
<td>IQ estimate; mean (SD) a</td>
<td>99.8 (19.5)</td>
<td>105.5 (19.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Treatment for:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- high blood pressure; % (n)</td>
<td>36.6 (75)</td>
<td>21.0 (26)</td>
<td>0.035</td>
</tr>
<tr>
<td>- diabetes mellitus; % (n)</td>
<td>10.7 (22)</td>
<td>4.8 (6)</td>
<td>0.069</td>
</tr>
<tr>
<td>Use of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- anti-depressive medication; % (n)</td>
<td>4.4 (9)</td>
<td>3.2 (4)</td>
<td>0.77</td>
</tr>
<tr>
<td>- benzodiazepines; % (n)</td>
<td>16.6 (34)</td>
<td>4.8 (6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Activities b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- employment; % (n)</td>
<td>13.7 (28)</td>
<td>21.8 (27)</td>
<td>0.067</td>
</tr>
<tr>
<td>- cognitively stimulating activities; mean (SD) c</td>
<td>4.3 (1.3)</td>
<td>4.4 (1.1)</td>
<td>0.86</td>
</tr>
<tr>
<td>- physical activities; mean (SD) d</td>
<td>7.3 (3.3)</td>
<td>8.4 (2.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Anxiety/Depression (HSCL);mean (SD) e</td>
<td>12.6 (10.9)</td>
<td>10.0 (9.1)</td>
<td>0.026</td>
</tr>
<tr>
<td>- possible depressive case; % (n) f</td>
<td>23.0 (47)</td>
<td>13.8 (17)</td>
<td>0.045</td>
</tr>
<tr>
<td>Fatigue score EORTC QLQ-C30; mean (SD) g</td>
<td>33.1 (21.7)</td>
<td>18.1 (15.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Variables related to lifetime estrogen exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- reproductive period (years); mean (SD)</td>
<td>34.3 (5.4)</td>
<td>33.0 (6.0)</td>
<td>0.048</td>
</tr>
<tr>
<td>- HRT (ever use); % (n)</td>
<td>16.6 (34)</td>
<td>18.5 (23)</td>
<td>0.66</td>
</tr>
<tr>
<td>Disease/treatment related variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Days since main surgery; mean (SD)</td>
<td>42.1 (20.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Current radiotherapy; % (n)</td>
<td>15.1 (31)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Physical functioning EORTC QLQ-C30; mean (SD) h</td>
<td>80.6 (16.0)</td>
<td>85.1 (16.7)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

a based on the Dutch version of the National Adult Reading Test.
b for patients: before diagnosis of cancer.
c range 2-8. higher score means more hours a day spent on these activities.
d range 2-14. higher score means higher frequency of these activities.
e range 0-100, higher score means more serious symptoms.
f ‘possible depressive case’ defined as a mean HSCL item score of ≥ 1.55.
g range 0-100, higher score means better functioning.

Table 1 shows sociodemographic, medical and psychological characteristics of the study sample. There were significant differences between the patient- and the control group regarding age and estimated IQ (P=0.006 and P=0.009 respectively). Furthermore, relatively more patients than healthy controls received treatment for hypertension.
(P=0.035) and reported to use benzodiazepines (P=0.001). The estimated ‘reproductive period’ was significantly longer in patients than in controls (P=0.048). In the year before the cognitive assessment (for patients: year before the diagnosis of BC), controls reported a higher frequency of physical activity (P=0.002). Self-reported physical functioning was higher in healthy controls than in patients (P= 0.032).

Patients reported more serious complaints regarding anxiety/depression and fatigue (P=0.026 and P<0.001, respectively). Significantly more patients (23.0%) than healthy controls (13.8%) scored in the ‘possibly depressive case’ range (HSCL mean item score ≥ 1.55, P=0.045).26

Factors associated with cognitive functioning before adjuvant systemic therapy

Results of the multiple regression analysis aiming to determine predictors for cognitive performance in the patient group are shown in table 2. For all, but one, cognitive domains, a lower age and a higher IQ were strong explanatory variables for better performance and explained 10% to 40% of the variance (R² adj .10 - .40; P<0.001). For working memory, age was not a predictor, but IQ alone explained 25% of the variance (R² adj .25, P<0.001).

Independent from age and IQ, the following variables contributed significantly to one or more cognitive domains (table 2): ongoing treatment for hypertension had a negative impact on verbal fluency and working memory performance; ongoing treatment for diabetes mellitus was predictive for worse executive functioning and a slower reaction speed; there was a positive impact of time daily spent on cognitively stimulating activities and performance on tasks for verbal memory, information processing speed, executive functioning and verbal fluency; more days since surgery were predictive for better visual memory performance, and a higher number of ‘reproductive years’ was predictive for worse executive functioning. The associated variables additionally explained 1 to 6% of the variance (R² adj. of the final models: 0.16 - 0.41; P <0.001).

Cognitive performance of patients compared to healthy controls

MANCOVA across the eight cognitive domains, aiming to compare cognitive functioning of the BC patients with cognitive functioning of healthy controls, showed significantly worse cognitive performance in the BC group, compared to the healthy control group (after
adjustment for age and IQ: F=3.8, P<0.001, Cohen’s d=0.62). Additional adjustment for the covariates associated with performance in the BC patient group, showed a reduction of the difference between BC patients and healthy controls (F=3.1, P=0.002, Cohen’s d=0.56). After additional adjustment for the remaining variables, MANCOVA showed a further reduction of the cognitive difference (F=2.2, P=0.03, Cohen’s d=0.48), but a statistically significant difference in overall cognitive performance between the patient group and the healthy control groups remained (see table 3).

Univariate ANCOVA’s for the eight different cognitive domains showed, after adjustment for all covariates, a significant difference on one cognitive domain (i.e. verbal fluency). BC patients performed worse than healthy controls (F=8.7, P=0.003, Cohen’s d=0.33, table 3).

Table 2. Multiple regression analysis in the BC patient group

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>R² adj.</th>
<th>Model</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td>.201</td>
<td>Age + IQ</td>
<td>-.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age + IQ + Cognitively stimulating activities</td>
<td>.17</td>
<td>0.01</td>
</tr>
<tr>
<td>Visual memory</td>
<td>.299</td>
<td>Age + IQ + Days since surgery</td>
<td>-.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age + IQ + Cognitively stimulating activities</td>
<td>.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Information processing speed</td>
<td>.400</td>
<td>Age + IQ + Cognitively stimulating activities</td>
<td>.13</td>
<td>0.03</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>.358</td>
<td>Age + IQ + Treatment for diabetes mellitus + cognitively stimulating activities + number of reproductive years</td>
<td>-.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age + IQ + Treatment for diabetes mellitus</td>
<td>.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age + IQ + Cognitively stimulating activities</td>
<td>.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Manual motor speed</td>
<td>.203</td>
<td>Age + IQ</td>
<td>-.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>.379</td>
<td>Age + IQ + Treatment for hypertension + cognitively stimulating activities</td>
<td>-.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age + IQ + Treatment for hypertension</td>
<td>.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age + IQ + Cognitively stimulating activities</td>
<td>.14</td>
<td>0.01</td>
</tr>
<tr>
<td>Reaction speed</td>
<td>.102</td>
<td>Age + IQ + Treatment for diabetes mellitus</td>
<td>-.18</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age + IQ + Treatment for hypertension</td>
<td>.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age + IQ + Treatment for diabetes mellitus</td>
<td>-.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Working memory</td>
<td>.245</td>
<td>IQ</td>
<td>.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IQ + treatment for hypertension</td>
<td>-.18</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Table 3. Cognitive domain scores and raw test scores of BC patients and healthy controls

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>BC Patients (n=205)</th>
<th>Healthy controls (n=124)</th>
<th>PK</th>
<th>PL</th>
<th>PM</th>
<th>Cohen’s d n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- RAVLT immediate 27 a</td>
<td>-11 (.89)</td>
<td>0 (.81)</td>
<td>0.42</td>
<td>0.31</td>
<td>0.26</td>
<td>0.13</td>
</tr>
<tr>
<td>- RAVLT delayed 27 a</td>
<td>21.2 (6.0)</td>
<td>22.1 (5.7)</td>
<td>0.67</td>
<td>0.61</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>- Visual association Test 28 b</td>
<td>6.1 (3.0)</td>
<td>6.3 (3.0)</td>
<td>0.36</td>
<td>0.33</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Visual memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- WMS immediate 29 c</td>
<td>-51 (1.2)</td>
<td>.0 (.95)</td>
<td>0.01</td>
<td>0.02</td>
<td>0.09</td>
<td>0.19</td>
</tr>
<tr>
<td>- WMS delayed 29 c</td>
<td>28.9 (6.3)</td>
<td>31.4 (5.4)</td>
<td>0.04</td>
<td>0.05</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Information processing speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stroop Card 1 30 d</td>
<td>-37 (87)</td>
<td>0 (.81)</td>
<td>0.04</td>
<td>0.11</td>
<td>0.24</td>
<td>0.13</td>
</tr>
<tr>
<td>- Stroop Card 2 30 d</td>
<td>50.0 (8.7)</td>
<td>46.8 (7.6)</td>
<td>0.09</td>
<td>0.13</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>- Trailmaking A 31 e</td>
<td>64.8 (11.2)</td>
<td>61.2 (10.3)</td>
<td>0.20</td>
<td>0.31</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Executive functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stroop Card 3 30 c</td>
<td>-48 (1.2)</td>
<td>0 (.86)</td>
<td>0.05</td>
<td>0.18</td>
<td>0.52</td>
<td>0.06</td>
</tr>
<tr>
<td>- Trailmaking B 31 e</td>
<td>123.1 (42.3)</td>
<td>107.9 (33.3)</td>
<td>0.09</td>
<td>0.27</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Manual motor speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- tapping dominant hand 32 f</td>
<td>-16 (89)</td>
<td>0 (.98)</td>
<td>0.64</td>
<td>0.74</td>
<td>1.0</td>
<td>0.00</td>
</tr>
<tr>
<td>- tapping non-dominant hand 32 f</td>
<td>51.2 (8.8)</td>
<td>52.2 (10.1)</td>
<td>0.24</td>
<td>0.26</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- animals 33 g</td>
<td>-.52 (.86)</td>
<td>0 (.83)</td>
<td>&lt;.001</td>
<td>0.001</td>
<td>0.003</td>
<td>0.33</td>
</tr>
<tr>
<td>- professions 33 g</td>
<td>20.3 (6.0)</td>
<td>23.1 (5.9)</td>
<td>0.01</td>
<td>0.03</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>- letters: DAT 34 h</td>
<td>16.3 (4.8)</td>
<td>19.3 (5.3)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Reaction speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- dominant hand 32 i</td>
<td>-37 (1.7)</td>
<td>0 (.94)</td>
<td>0.27</td>
<td>0.59</td>
<td>0.45</td>
<td>0.09</td>
</tr>
<tr>
<td>- non-dominant hand 32 i</td>
<td>330 (113)</td>
<td>309 (58)</td>
<td>0.50</td>
<td>0.94</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Letter number sequencing 35 j</td>
<td>-41 (97)</td>
<td>0 (1.0)</td>
<td>0.03</td>
<td>0.07</td>
<td>0.22</td>
<td>0.14</td>
</tr>
<tr>
<td>Overall analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean values shown, with standard deviation in parentheses.

- Rey auditory verbal learning test (Dutch shortened version), total number of words after 3 trials and total number of words in delayed recall.
- Visual Association Test, number of correct responses.
- Wechsler Memory Scale revised – visual memory subtest, points awarded according to scoring criteria.
- Stroop Color Word Test, seconds to complete task (lower scores represent better performance).
- Trailmaking Test, seconds to complete task (lower scores represent better performance).
- Fepsy Finger tapping, mean of 5 trials of 10 seconds.
- Category Fluency (animals/professions), total of words produced in one minute.
- Letter fluency (D,A,T), number of words produced in 3 minutes (1 minute for each letter).
- Fepsy Reaction times, milliseconds (lower scores represent better performance).
- WAIS III Letter-number sequencing, number of correct responses.
- P-value corrected for age/IQ.
- P-value corrected for age/IQ, treatment for diabetes mellitus/high blood pressure, frequency of participating in cognitive stimulating activities, number of ‘reproductive years’.
- P-value corrected for all covariates (see table 1).
- Cohen’s d after adjustment for all covariates: <0.20: small effect, 0.20-0.80: medium effect, >.80: large effect, range 0-2.
Discussion

Recent studies evaluating the cognitive effects of adjuvant systemic therapies in BC patients predominantly have a prospective design, including neuropsychological assessments before the start of adjuvant systemic treatment. Although the majority of these studies showed that a subset of BC patients performed below expected levels already before the start of adjuvant therapy, little is known about possible explanations of this pre-treatment cognitive impairment. In order to increase the understanding of the cognitive impairment prior to the start of systemic treatment, the first study aim was to identify predictors for cognitive performance in a group of postmenopausal BC patients. We observed that ‘ongoing treatment for diabetes mellitus’, ‘ongoing treatment for hypertension’, ‘less hours spent daily on cognitively stimulating activities’, ‘less days since surgery’ and ‘more reproductive years’ were predictive for worse performance on one or multiple cognitive domains, independent of the strong predictors age and IQ. The (combinations of) identified predictors explained a modest 1 to 6% of the variance in cognitive performance in addition to age and IQ.

Our findings of associations between these variables and cognitive performance generally are consistent with literature data. Diabetes mellitus and/or hypertension are known to be associated with lower cognitive functioning, but the role of treatments for these conditions in preventing cognitive disorders is still a matter of debate. Our observation that patients spending more time on cognitively stimulating activities had a better cognitive performance is supported by data of Wilson et al. who used a similar self-report measure for the frequency assessment of cognitively stimulating activities. The positive relationship between ‘days since surgery’ and cognitive performance that we observed has not been reported earlier in BC patients, but indicates that effects of earlier treatments might play a role in cognitive performance before the start of adjuvant systemic treatment. In fact, the topic of postoperative cognitive dysfunction (POCD) has not been studied thoroughly in BC patients, but from studies in other patient groups it is known that POCD is present in the first weeks after surgery in a significant proportion of patients. In one study in BC patients, time since surgery did not predict for cognitive impairment, but more patients who had undergone a lumpectomy or mastectomy had impaired cognitive functioning compared to patients who underwent biopsy only. In another study, the duration of anesthesia, and the type of surgery (lumpectomy versus mastectomy) were not associated with cognitive performance. The observation in our
study that ‘days since surgery’ was specifically associated with visual memory performance was not expected. Further research should determine whether this is a coincident finding.

We observed an inverse relationship between ‘reproductive period’ and executive functioning in the BC patient group. Although the influence of estrogen on cognitive function has been established in a major area of fundamental and clinical research, studies evaluating the impact of lifetime estrogen exposure on cognitive functioning yield incongruent results reporting beneficial effects, no effects, as well as detrimental effects. Notwithstanding the variability in study results up till now on this issue, lifetime estrogen exposure might be an important factor in cognitive studies in BC patients, given the described differences in hormonal history between BC patients and healthy controls.

Our second aim was to compare cognitive functioning in BC patients with cognitive functioning of healthy controls. We observed lower overall cognitive performance in the BC patient group than in the healthy control group. Considering the eight cognitive domains separately, the only significantly lower performance in BC patients versus controls was found in the verbal fluency domain. The medical and psychological variables that were associated with cognitive performance in the BC patient group could partly explain this overall difference in cognitive functioning. Beside these relevant predictors, a number of additional variables contributed to the overall cognitive difference between BC patients and healthy controls. This may be caused by differences in strength of relationships between these variables and cognitive performance in the patient and healthy control group, or by different distributions of these variables in the patient group compared to the healthy control group. Nevertheless, after adjustment for the potential explanatory factors, a significantly lower cognitive performance was observed in BC patients versus healthy controls.

The current results raise several issues for future research regarding cognitive effects of cancer treatments. Our findings show that several medical and psychological factors have an impact on cognitive functioning. The predictive value of the variables might be dependent on the particular nature of the study, such as the time since diagnosis, earlier treatments, or the age of the participants. For example, the impact of comorbidities such as diabetes mellitus might be more prominent in older patients compared to younger
patients.\textsuperscript{43} Moreover, medical and psychological factors which are associated with cognitive performance might not be equally distributed between study groups. Particularly in non-randomized studies, differences in potentially important factors are easily introduced, for example due to selection bias, and might hinder proper interpretation of cognitive outcomes. In the instance that only published norms are used, such relevant information about medical and psychological variables is generally lacking. Notwithstanding the potential importance of medical and psychological variables for cognitive functioning, they only partly explained the observed difference in cognitive functioning between BC patients and healthy controls. This justifies further studies into additional potentially explanatory factors.

Importantly, apart from understanding the phenomenon of cognitive impairment preceding adjuvant systemic therapy, this study implicates that baseline cognitive differences between groups have to be taken into account in studies evaluating the cognitive effects of cancer treatments. In cross-sectional studies, with only a post-treatment assessment, adjustment for pre-treatment cognitive differences is impossible, but our results suggest that adjustment for medical and psychological variables might be valuable, particularly in non-randomized studies.

The strengths of our study on cognitive functioning before the start of adjuvant systemic therapy are on the one hand the large number of BC patients and healthy controls compared to other studies in this research field, and on the other hand the wide range of neuropsychological tests used. Also, we were able to examine the contribution of many possible covariates with respect to cognitive functioning, and to adjust for these variables in the analyses.

A limitation of this study is that the information regarding specific co-morbidities, the use of co-medication and (ever) use of HRT was self-reported and had a dichotomic character. Detailed information about specific agents used, dosages, time on treatment and the extent to which the underlying disease (for example hypertension or depression) was adequately treated was not included, possibly being of influence on the effects we found on cognitive functioning. In future studies, the inclusion of more detailed information on important variables might increase our understanding of the impact of these variables on cognitive functioning. Another limitation is the selection method of the control group. The
healthy controls were invited by the participating patients out of their circle of friends and family. This type of control group was chosen for minimizing sociodemographic differences between patients and healthy controls. Nevertheless, we had the impression that patients, in general, tended to invite a relatively young and healthy friend or relative, inducing some degree of selection bias. As a result, the healthy control group was not completely comparable with the patient group with respect to age, IQ, occurrence of co-morbidities and health-related variables such as frequency of physical activity. As some of these factors might be related to BC risk as well as to cognitive functioning, this might have had impact on the observed results.

In conclusion, in our postmenopausal BC patient group, several medical, psychological and treatment-related variables were associated with cognitive performance before the start of adjuvant systemic therapy. Overall cognitive functioning in our BC patient group was lower compared to cognitive functioning of our healthy control group. Combinations of medical and psychological factors partly explained this lower cognitive functioning. Our data underline the importance of (1) future research into the etiology of this lower cognitive performance in BC patients before the start of adjuvant systemic treatment, and (2) adjustment for pre-treatment cognitive differences between study groups when evaluating effects of cancer treatments on cognitive functioning.

Acknowledgements

We are indebted to all patients, healthy controls as well as physicians and research nurses of 38 Dutch hospitals that participated in this cognitive study. We are also grateful to the Datacenter Heelkunde of the Leiden University Medical Center for organizational support and to M. Weevers, S. Leering and A. van Nuland for helping collecting the data. This original work was supported by an independent research grant from Pfizer, grant number 56850.
Chapter 4

Reference List


(38) Cukierman-Yaffe T, Gerstein HC, Williamson JD et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other


Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal breast cancer patients: results form the neuropsychological side study of the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial

Abstract

**Purpose:** To evaluate the influence of adjuvant tamoxifen and exemestane on cognitive functioning in postmenopausal patients with breast cancer (BC).

**Patients and Methods:** Neuropsychological assessments were performed before the start (T1) and after 1 year of adjuvant endocrine treatment (T2) in Dutch postmenopausal patients with BC, who did not receive chemotherapy. Patients participated in the international Tamoxifen and Exemestane Adjuvant Multinational trial, a prospective randomized study investigating tamoxifen versus exemestane as adjuvant therapy for hormone-sensitive BC.

**Results:** Participants included 80 tamoxifen users (mean age, 68.7 yrs, range 51 to 84), 99 exemestane users (mean age, 68.3 yrs, range 50 to 82) and 120 healthy controls (mean age, 66.2 yrs; range 49-86). At T2, after adjustment for T1 performance, exemestane users did not perform statistically significantly worse than healthy controls on any cognitive domain. In contrast, tamoxifen users performed statistically significantly worse than healthy controls on verbal memory ($P<.01$, Cohen's $d = .43$) and executive functioning ($P=.01$, Cohen's $d = .40$), and statistically significantly worse than exemestane users on information processing speed ($P=.02$, Cohen's $d = .36$). With respect to visual memory, working memory, verbal fluency, reaction speed and motor speed, no significant differences between the three groups were found.

**Conclusion:** After 1 year of adjuvant therapy, tamoxifen use is associated with statistically significant lower functioning in verbal memory and executive functioning, while exemestane use is not associated with statistically significant lower cognitive functioning in postmenopausal BC patients. Our results accentuate the need to include assessments of cognitive effects of adjuvant endocrine treatment in long-term safety studies.
Introduction

Adjuvant endocrine therapy is widely prescribed for patients with hormone-sensitive breast cancer (BC) and contributes to an improved survival.\(^1\) Ongoing trials are exploring the optimal duration of adjuvant endocrine therapy, as well as the most effective choice and sequence of agents.\(^2\) Although generally well tolerated, endocrine treatments have side effects which are of clinical concern\(^3\) and predictive for non-adherence.\(^4\) The toxicity profiles are class- and agent-specific, and concern menopausal symptoms, effects on bone density, changes in lipid profile, increased risk of endometrial cancer, cardiovascular disease and venous thrombosis.\(^5\)

Whether the various endocrine treatments affect cognitive functioning is largely unknown. Preclinical data indicate that estrogens exert neurotrophic and neuroprotective actions in the brain.\(^6\) Although the mechanisms of action of estrogens in the brain are not completely understood, evidence is growing that estrogens favor neuronal differentiation and survival by acting through estrogen receptors (ERs).\(^7\) As ERs are present in the hippocampus and the frontal lobe\(^8\), structures that are important for cognitive functioning, it is plausible that estrogens are involved in cognitive functioning.

From neuropsychological studies, partial support for the neuroprotective influence of estrogens can be derived. For example, estrogen deprivation following removal of the ovaries in premenopausal women was associated with decreased verbal memory performance, while estrogen replacement therapy (ERT) in this setting was associated with stable cognitive performance.\(^9\) In addition, a recent case-control study suggested that long-term estrogen deprivation due to premature menopause after ovariectomy increases the risk for dementia later in life.\(^10\)

Harmful effects of estrogens on the brain have also been suggested. In a randomized, placebo-controlled trial ERT increased the risk of dementia and stroke in women over 65 years of age,\(^11,12\) suggesting that estrogens are only neuroprotective during a critical time period around menopause and have no, or even detrimental effects in elderly women.\(^13,14\) Furthermore, neuropsychological studies suggest that not all cognitive functions are equally influenced by estrogens, but that the influence mainly concerns aspects of memory, information processing speed and executive functioning.\(^15\)
In view of the literature evoking an effect of estrogens on brain functioning, it is theoretically plausible that endocrine treatment for postmenopausal BC, aiming at estrogen deprivation, also might influence brain functioning and cognition. However, only few and predominantly small studies evaluated such effects. Generally, these studies provided indications for small detrimental effects of the Selective Estrogen Receptor Modulator (SERM) tamoxifen on cognition, but yielded inconclusive results with respect to the aromatase inhibitor (AI) anastrozole.

In this report we describe the results of a prospective study on the impact of tamoxifen and the AI exemestane on cognitive functioning in 179 Dutch postmenopausal BC patients, participating in the randomized Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial. It was hypothesized that both tamoxifen and exemestane would detrimentally affect certain cognitive functions. We exploratory evaluated possibly distinctive effects on cognition of both agents. Furthermore, given the potential age-dependency of the effects of estrogen on cognitive functioning, we investigated the cognitive effects of tamoxifen and exemestane in younger (≤65 yrs) and older (>65 yrs) patients separately.

**Patients and methods**

**Study population and procedure**

Eligible patients were Dutch postmenopausal women participating in the TEAM trial; an international, open label, randomized study comparing the efficacy and safety of 5 years of adjuvant exemestane (25 mg/day) with 2,5-3 years of tamoxifen (20 mg/day) followed by 2-2,5 years of exemestane.

Extended data on in- and exclusion criteria of the TEAM trial have been described elsewhere. In short, patients had histologically confirmed adenocarcinoma of the breast, positive estrogen and/or progesterone receptor status, and had undergone surgery with a curative intent. For this neuropsychological side study additional exclusion criteria included: adjuvant chemotherapy, not being fluent in the Dutch language, Central Nervous System (CNS) disease or signs of dementia according to a dementia screening tool (7 minutes screen). In order to take into account test-retest effects of neuropsychological tests, we also included a control group consisting of healthy female friends or relatives.
having approximately the same age as the participating TEAM patients. For this healthy control group, we aimed for a sample size of at least the sample size of the patient groups. Inclusion criteria for controls were: postmenopausal status, no history of CNS disease or malignant disease, fluent in the Dutch language and no signs of dementia according to the dementia screening tool. The neuropsychological study was approved by the central review board (Erasmus MC, Rotterdam) and the local medical ethic committees of all participating hospitals. All participants provided written informed consent.

**Assessment**

Initial neuropsychological assessments (T1) were performed after definite breast surgery, and immediately before the start of adjuvant endocrine treatment. This point in time was chosen in order to minimize potential effects of other treatments on cognition in the interval between T1 and T2. Follow-up assessments were conducted after 1 year of endocrine treatment (T2). Healthy control women underwent the same assessments with a similar time interval of 1 year.

**Cognitive tests**

A comprehensive test battery, existing of 18 test indices, was designed to assess a broad range of cognitive functions (table 1). All tests were classified in one of eight cognitive domains. The Dutch Adult Reading Test was used to estimate premorbid verbal intelligence. Tests were selected for reliability, validity, sensitivity for effects of hormones and suitability for older age groups.

**Anxiety/depression, fatigue and menopausal symptoms**

Data on anxiety/depression, fatigue and menopausal symptoms were included in the analyses because these symptoms (1) might act as confounders in the analysis of cognitive performance and (2) might be different at T1 and T2. For measuring symptoms of anxiety/depression, the 25-item Hopkins Symptom Checklist (HSCL) was used; and for fatigue, the 3-item fatigue subscale of the EORTC QLQ-C30. Menopausal symptoms were assessed by the 18-item Endocrine Subscale of the Functional Assessment of Cancer Therapy–Breast questionnaire (FACT B-ES). Participants rated all items on a 4-point (HSCL, EORTC QLQ-C30) or 5-point scale (FACT B-ES). Results of self-reported cognitive functioning will be reported separately.
### Table 1. Summary of cognitive test measures and outcome variables

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Cognitive tests</th>
<th>Outcome variable</th>
<th>Score range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal memory</strong></td>
<td>Rey auditory verbal learning test[^28] (Dutch shortened version) [^29]</td>
<td>1. Total of 3 trials</td>
<td>0-45</td>
</tr>
<tr>
<td></td>
<td>Visual Association Test[^29]</td>
<td>2. Total for long delay trial</td>
<td>0-15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Total of 2 trials</td>
<td>0-24</td>
</tr>
<tr>
<td><strong>Visual memory</strong></td>
<td>Wechsler Memory Scale revised – visual memory subtest[^30]</td>
<td>4. Points awarded according to scoring criteria</td>
<td>0-41</td>
</tr>
<tr>
<td></td>
<td>1. Immediate recall</td>
<td>5. Points awarded according to scoring criteria</td>
<td>0-41</td>
</tr>
<tr>
<td></td>
<td>2. Delayed recall</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Information processing</strong></td>
<td>Stroop Card 1[^31]</td>
<td>6. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Stroop Card 2[^31]</td>
<td>7. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Trailmaking A[^32]</td>
<td>8. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td><strong>Executive functioning</strong></td>
<td>Stroop Card 3[^31]</td>
<td>9. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Trailmaking B[^32]</td>
<td>10. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td><strong>Manual motor speed</strong></td>
<td>Fepsy Finger tapping:[^33]</td>
<td>11. Mean score of 5 trials of 10 seconds</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>1. dominant hand</td>
<td>12. Mean score of 5 trials of 10 seconds</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>2. non-dominant hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal fluency</strong></td>
<td>Letter fluency (D,A,T)</td>
<td>13. Total score of 3 letters/1 minute each</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Category Fluency (Animals/professions)</td>
<td>14. Total score animals/1 minute</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15. Total score professions/1 minute</td>
<td>0+</td>
</tr>
<tr>
<td><strong>Reaction speed</strong></td>
<td>Fepsy Reaction times:[^33]</td>
<td>16. Mean msec/30 trials</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>1. dominant hand</td>
<td>17. Mean msec/30 trials</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>2. non-dominant hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td>WAIS III Letter-number sequencing[^36]</td>
<td>18. Total correct trials</td>
<td>0-21</td>
</tr>
</tbody>
</table>

**Statistical analysis**

SPSS for windows version 15.0 (SPSS, Chicago, IL) was used for all analyses. Raw cognitive test scores were converted to standardized Z-scores based on the mean and standard deviation of the healthy control group. For T1, healthy control group data at T1 were used; for T2, healthy control group data at T2.

To decrease the number of outcome variables, the 18 Z-scores were combined into eight cognitive domain scores, expressed as the mean Z-score of tests that made up the particular cognitive domain. By definition, mean Z-scores and cognitive domain scores of the healthy control group were zero both at T1 and T2, and the T2 scores discounted for test-retest effects. Data from questionnaires were converted to scores according to standard scoring rules.
Changes from T1 to T2 and between groups were analyzed by using univariate analyses of covariance (ANCOVA) in which, for each of eight cognitive domains, the T2 score was the dependent variable and the T1 score was the covariate. We chose for this method for its demonstrated power and its adjustment for baseline imbalances. Both ‘intent-to-treat’ (patient groups defined by the allocated agent) and ‘as-treated’ (groups defined by actual use of tamoxifen or AIs) analyses were carried out. Both treatment groups were compared separately with the healthy control group, and the tamoxifen group was compared with the exemestane group.

Because anxiety/depression, fatigue and menopausal symptom ratings might act as confounders, the ANCOVA procedure was repeated on the understanding that both T1 scores and these variables served as predictors.

To investigate possible age differences with respect to the cognitive effects of tamoxifen and exemestane, we repeated the ANCOVA procedure, adjusted for T1 scores in two subgroups separately: (1) women age ≤65 years and (2) women older than 65 years. Effect-sizes were expressed by Cohen’s d. For all analyses, a two-sided P-value less than .05 was required for significance. P-values for the direct comparison between tamoxifen and exemestane should be interpreted as exploratory in nature, as no hypothesis could be formulated on the basis of the literature for differences between the two therapies in effect on cognition. The sample-sizes of the two patient groups (80 and 99 persons, respectively) provided 76% power (type I error rate of 5% and 2-sided tests) to detect a between-group difference of 0.4 standard deviation. This was a lower bound for the power obtained by the healthy control group, which had a sample-size of 120.

**Results**

**Patients and controls**

Ninety-two patients allocated to tamoxifen, 114 patients allocated to exemestane and 124 healthy controls underwent cognitive assessments at T1. Data at T2 were provided by 90% of the participants (80 tamoxifen users, 99 exemestane users and 120 healthy controls). More patients than healthy controls were lost to follow-up (12.7% versus 3.2%, respectively), without a statistically significant difference between tamoxifen (13.0%) and exemestane (12.4%) users (figure 1). The participants who were lost to follow-up were
significantly older (72.3 versus 67.6 years; \( P = .01 \)) and had a lower intelligence quotient (93.9 versus 102.7; \( P = .02 \)) than participants who completed both assessments.

### Table 2. Sociodemographics of the tamoxifen users, the exemestane users and the healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen users (n= 80)</th>
<th>Exemestane users (n=99)</th>
<th>Healthy controls (n=120)</th>
<th>p-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>68.7 (7.6)</td>
<td>68.3 (6.8)</td>
<td>66.2 (7.9)</td>
<td>.03(^b)</td>
</tr>
<tr>
<td>Range</td>
<td>51-84</td>
<td>50-82</td>
<td>49-86</td>
<td></td>
</tr>
<tr>
<td><strong>IQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>100.7 (20.0)</td>
<td>100.5 (18.6)</td>
<td>105.8 (19.0)</td>
<td>.07</td>
</tr>
<tr>
<td><strong>T1-T2 interval in months; Mean (SD)</strong></td>
<td>12.4 (1.2)</td>
<td>12.2 (1.4)</td>
<td>12.3 (0.6)</td>
<td>.25</td>
</tr>
<tr>
<td><strong>Underwent Radiotherapy % (n)</strong></td>
<td>58.8 (47)</td>
<td>68.7 (68)</td>
<td>-</td>
<td>.16</td>
</tr>
<tr>
<td><strong>Ever-use of hormone replacement therapy % (n)</strong></td>
<td>17.5 (14)</td>
<td>20.2 (20)</td>
<td>19.2 (23)(^d)</td>
<td>.79</td>
</tr>
<tr>
<td><strong>Self-reported adherence % (n)</strong>(^c)</td>
<td>100%</td>
<td>70 (56)</td>
<td>75 (74)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>99-100%</td>
<td>19 (15)</td>
<td>21 (21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95-99%</td>
<td>6 (5)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>83-94%</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;83%</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) P-values for ANOVA (for age, IQ and T1-T2 interval) and Chi-square test (for self-reported adherence).

\(^b\) Post-hoc tests: tamoxifen versus controls: \( p = .03 \); exemestane versus controls: \( p = .04 \); tamoxifen versus exemestane: \( p = .71 \).

\(^c\) Self-reported therapy adherence was assessed by two questions: (1) have you (temporarily) stopped taking the study medication, and if so, what was/were the start- and the end date(s) of these period(s)? and (2) how often (each week, month or in the whole interval between T1 and T2) have you forgotten to take the study medication? Self-reported adherence to the study medication was calculated as the proportion of the days that the patients reported to have taken their tablets over the period between T1 and T2.

\(^d\) \( n = 119 \).

After controlling for age and IQ, there were no statistically significant differences in cognitive performance (at T1) between participants who were lost to follow-up and participants who completed both assessments. Furthermore, both groups did not differ significantly with respect to anxiety/depression and fatigue ratings (at T1).

Between T1 and T2, the endocrine therapy was changed by 12 patients (6.7%). Six tamoxifen users changed to exemestane, and six exemestane users changed to either
tamoxifen (n=4), anastrozole (n=1) or letrozole (n=1). The predominant reason for changing endocrine therapy was bothering adverse effects.

Self-reported adherence to the study medication was not statistically significant different between tamoxifen and exemestane users (table 2). In view of the literature that considers taking medication for more than 80% of the days as an acceptable adherence, all patients could be regarded as adherent.4

Cognitive test results: Baseline assessment (T1)

The baseline cognitive domain scores of patients are included in table 3 for illustrative purposes, and have been described and discussed elsewhere.39 In summary, the patient group, as a whole, had after adjustment for covariates such as age, IQ, ongoing treatment for hypertension or diabetes mellitus, and anxiety/depression, a significantly worse overall cognitive functioning compared to healthy controls (P=.03). Considering the eight cognitive domains separately, the only significant lower performance in the patient group was in the verbal fluency domain (P<.01).

Follow-up assessment (T2)

Raw test scores of T1 and T2 are presented in table 3, anxiety/depression, fatigue and menopausal symptoms ratings in table 4. The results of the intent-to-treat analyses are shown in table 5. After 1 year of adjuvant therapy and adjusting for T1 scores, exemestane users did not perform significantly worse than healthy controls on any of the eight cognitive domains. In contrast, tamoxifen users performed worse than healthy controls on verbal memory (P<.01, Cohen’s d=.43) and executive functioning (P=.01, Cohen’s d=.40). Furthermore, compared to exemestane users, tamoxifen users scored lower on information processing speed (P=.02, Cohen’s d=.36). For visual memory, reaction speed, motor speed, working memory and verbal fluency no significant differences between the groups were found.

The ‘as-treated’ analysis showed significantly worse functioning in tamoxifen users compared to healthy controls on the same cognitive domains, with slightly larger effect-sizes (verbal memory: P<.01, Cohen’s d=.46; executive functioning: P<.01, Cohen’s d=.44), and worse cognitive functioning in tamoxifen users compared to exemestane users not
only on information processing speed \((P<.01, \text{Cohen's } d=.47)\), but also on executive functioning \((P=.03, \text{Cohen's } d=.34; \text{data not shown})\). Additional adjustment for anxiety/depression, fatigue and menopausal symptom scores did not change these results.

Exploratory intent-to-treat analyses showed that in the younger age group \((\leq 65 \text{ years})\) tamoxifen users \((n=30)\) performed significantly worse than healthy controls \((n=60)\) on executive functioning \((P=.01, \text{Cohen's } d=.54)\), while in the older age group \((>65 \text{ years})\) tamoxifen users \((n=50)\) performed worse than healthy controls \((n=60)\) on verbal memory \((P<.01, \text{Cohen's } d=.58)\) and information processing speed \((P=.03, \text{Cohen's } d=.44)\). In addition, only in the older age group tamoxifen users performed worse than exemestane users \((n=64)\) on information processing speed \((P=.01, \text{Cohen's } d=.54)\) (data not shown). For all significant differences, the effect-sizes were small-to-medium.

**Discussion**

This prospective study evaluated cognitive functioning during adjuvant therapy with tamoxifen or exemestane in postmenopausal patients with hormone-sensitive BC. We observed that 1 year of exemestane treatment did not result in significantly negative effects on cognitive functioning. In contrast, 1 year of tamoxifen treatment was associated with worse performance regarding verbal memory and executive functioning. For information processing speed, we observed a significant difference between tamoxifen and exemestane users due to an increased performance in the exemestane group and a decreased performance in the tamoxifen group. The effect-sizes of all significant differences were small-to-medium and were higher in the ‘as treated’ analyses compared with the intent-to-treat analyses, confirming the robustness of the effects. Adjustment for menopausal symptoms, anxiety/depression ratings and fatigue did not influence the results.
**Effects of tamoxifen and exemestane on cognitive functioning**

**Figure 1. Participant flowchart**

Randomized in the TEAM trial and invited for neuropsychological study: n=331

Refused consent: n=85
- not interested: n=26
- too burdensome: n=59

Reason of non-participation unknown: n =40

Enrolled in the neuropsychological side study: n=206

Enrolled in the neuropsychological side study: n=206

**Baseline**

Tamoxifen users n=92
- Lost to follow-up (n=12)
  - died (n=3)
  - progressive disease (n=1)
  - had chemotherapy (n=1)
  - recent death in family (n=2)
  - unrelated health problems (n=2)
  - lack of interest (n=3)

Exemestane users n=114
- Lost to follow-up (n=15)
  - progressive disease (n=3)
  - failed dementia screening (n=1)
  - > 20% missing test scores (n=1)
  - lack of interest (n=10)

Healthy controls N=124
- Lost to follow-up (n=4)
  - health problems (n=2)
  - lack of interest (n=2)

**Follow-up**

Tamoxifen users n=80

Exemestane users n=99

Healthy controls n=120

REF: Participant flowchart
<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Baseline (T1)</th>
<th>One year (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAM (n=80)</td>
<td>EXE (n=99)</td>
</tr>
<tr>
<td><strong>Verbal memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- RAVLT immediate</td>
<td>-0.02 (.87)</td>
<td>-0.13 (.85)</td>
</tr>
<tr>
<td>- RAVLT delayed</td>
<td>22.6 (5.8)</td>
<td>21.0 (6.0)</td>
</tr>
<tr>
<td>- Visual association Test</td>
<td>6.5 (2.9)</td>
<td>6.1 (3.0)</td>
</tr>
<tr>
<td><strong>Visual memory</strong></td>
<td>20.6 (3.5)</td>
<td>20.6 (2.9)</td>
</tr>
<tr>
<td>- WMS immediate</td>
<td>-0.53 (1.13)</td>
<td>-0.40 (1.11)</td>
</tr>
<tr>
<td>- WMS delayed</td>
<td>29.0 (6.3)</td>
<td>30.0 (6.0)</td>
</tr>
<tr>
<td><strong>Processing speed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stroop Card 1</td>
<td>-0.38 (.94)</td>
<td>-0.40 (.88)</td>
</tr>
<tr>
<td>- Stroop Card 2</td>
<td>50.2 (9.1)</td>
<td>49.3 (7.8)</td>
</tr>
<tr>
<td>- Trailmaking A</td>
<td>64.0 (10.8)</td>
<td>64.4 (11.1)</td>
</tr>
<tr>
<td><strong>Executive functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stroop Card 3</td>
<td>-0.39 (1.01)</td>
<td>-0.51 (1.34)</td>
</tr>
<tr>
<td>- Trailmaking B</td>
<td>118.9 (30.6)</td>
<td>123.9 (48.8)</td>
</tr>
<tr>
<td><strong>Manual motor speed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- tapping dominant hand</td>
<td>-0.10 (.92)</td>
<td>-0.12 (.88)</td>
</tr>
<tr>
<td>- tapping non-dominant hand</td>
<td>51.3 (9.4)</td>
<td>51.7 (8.7)</td>
</tr>
<tr>
<td><strong>Verbal fluency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- animals</td>
<td>-0.52 (.94)</td>
<td>-0.52 (.82)</td>
</tr>
<tr>
<td>- professions</td>
<td>20.3 (9.1)</td>
<td>20.7 (5.9)</td>
</tr>
<tr>
<td>- letters: DAT</td>
<td>16.4 (5.2)</td>
<td>16.3 (4.5)</td>
</tr>
<tr>
<td><strong>Reaction speed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- dominant hand</td>
<td>-0.62 (2.5)</td>
<td>-0.23 (.95)</td>
</tr>
<tr>
<td>- non-dominant hand</td>
<td>339 (163)</td>
<td>322 (58)</td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Letter number sequencing</td>
<td>-0.40 (1.06)</td>
<td>-0.36 (.87)</td>
</tr>
</tbody>
</table>

TAM = tamoxifen users; EXE = exemestane users; CON = Healthy controls. Cognitive domain scores are expressed as Z-scores. See Statistical analysis-section for information about the composition of the Z-scores. SD = standard deviation; total number of words after 3 trials; number of correct responses; seconds to complete task (lower scores represent better performance); mean of 5 trials of 10 seconds; total of words produced in 1 minute; total number of words produced in 3 minutes (1 minute for each letter); milliseconds (lower scores represent better performance).
Table 4. Anxiety/depression, fatigue and menopausal symptoms scores at T1 and T2

<table>
<thead>
<tr>
<th>Psychosocial and endocrine measures</th>
<th>Baseline (T1)</th>
<th>One year (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAM (n=80)</td>
<td>EXE (n=99)</td>
</tr>
<tr>
<td>anxiety/depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSCL; mean (SD)</td>
<td>13.9 (11.4)</td>
<td>11.7 (10.5)</td>
</tr>
<tr>
<td>fatigue:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ C-30; mean (SD)</td>
<td>33.6 (21.5)</td>
<td>32.4 (22.3)</td>
</tr>
<tr>
<td>endocrine symptoms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACT-B ES; mean (SD)</td>
<td>62.1 (6.8)</td>
<td>63.1 (5.8)</td>
</tr>
</tbody>
</table>

\(^{1}\) range 0-100, higher score means more serious symptoms.
\(^{2}\) range 0-72. higher score means less serious symptoms.
<table>
<thead>
<tr>
<th>Cognitive domain (mean, SD)</th>
<th>Baseline (T1)</th>
<th>Follow-up (T2)</th>
<th>TAM-CON</th>
<th>EXE-CON</th>
<th>TAM-EXE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tamoxifen users (n=80)</td>
<td>Exemestane users (n=99)</td>
<td>Tamoxifen users (n=80)</td>
<td>Exemestane users (n=99)</td>
<td>P&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>-.02 (.87)</td>
<td>-.13 (.85)</td>
<td>-.23 (.97)</td>
<td>-.21 (.97)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Visual memory</td>
<td>-.53 (1.13)</td>
<td>-.40 (1.11)</td>
<td>-.49 (1.15)</td>
<td>-.31 (1.02)</td>
<td>.48</td>
</tr>
<tr>
<td>Processing speed</td>
<td>-.38 (.94)</td>
<td>-.40 (.88)</td>
<td>-.46 (1.10)</td>
<td>-.28 (.95)</td>
<td>.17</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>-.39 (1.01)</td>
<td>-.51 (1.34)</td>
<td>-.60 (1.20)</td>
<td>-.53 (1.39)</td>
<td>.01</td>
</tr>
<tr>
<td>Manual motor speed</td>
<td>-.10 (.92)</td>
<td>-.12 (.88)</td>
<td>-.19 (.99)</td>
<td>-.21 (1.02)</td>
<td>.17</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>-.52 (.94)</td>
<td>-.52 (.82)</td>
<td>-.51 (.83)</td>
<td>-.47 (.75)</td>
<td>.28</td>
</tr>
<tr>
<td>Reaction speed</td>
<td>-.62 (2.5)</td>
<td>-.23 (.95)</td>
<td>-.50 (1.40)</td>
<td>-.24 (1.13)</td>
<td>.07</td>
</tr>
<tr>
<td>Working memory</td>
<td>-.40 (1.06)</td>
<td>-.36 (1.87)</td>
<td>-.36 (1.24)</td>
<td>-.39 (1.09)</td>
<td>.55</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cognitive domain scores are expressed as Z-scores. See Statistical analysis-section for information about the composition of the Z-scores.

Values in this table represent the distance to the mean score of the healthy control group expressed in terms of SD’s (Mean Z-scores of the healthy control group are 0, SD’s are 1).

<sup>b</sup> p-value for ANCOVA of cognitive domain scores at T2, adjusted for cognitive domain scores at T1.

<sup>c</sup> p-value for ANCOVA of cognitive domain scores at T2, adjusted for cognitive domain scores at T1, anxiety/depression, fatigue and menopausal symptoms at T2.

<sup>d</sup> Effect size expressed as Cohen’s d: .20: small effect, .20-.80: medium effect, >.80: large effect.
The observed differences between tamoxifen and exemestane with respect to cognitive effects might imply different mechanisms of action of the drugs in the brain. Tamoxifen exerts tissue-dependent estrogenic and anti-estrogenic actions after binding to the estrogen receptor (ER), but whether it has estrogenic or anti-estrogenic qualities on brain tissue is not known. Our results support the results of earlier studies performed in postmenopausal BC patients, which suggested a detrimental effect of tamoxifen on cognitive functioning. Also, the cognitive domains that were vulnerable for the effects of tamoxifen in our study (verbal memory, information processing speed and executive functioning) overlap with those found affected in earlier studies, and indeed are associated with brain structures known to be rich of ERs (i.e. hippocampus and frontal lobe).

The AI exemestane causes nearly complete estrogen deprivation by blocking estrogen biosynthesis. Our results suggest that in postmenopausal BC patients such estrogen deprivation does not result in measurable cognitive effects. As our study is the first to evaluate the cognitive effects of exemestane our data can only be compared with results obtained from studies with the AI anastrozole. For anastrozole, however, data about its impact on cognition are conflicting. One cross-sectional study suggested detrimental effects on verbal memory and information processing speed in BC patients using anastrozole and/or tamoxifen (n=94) compared to healthy controls (n=35). Another cross-sectional study in BC patients suggested detriments on verbal and visual memory in anastrozole users (n=15) compared to tamoxifen users (n=16). A prospective study suggested that BC patients taking anastrozole (n=14) were more likely to show cognitive decline after 5-6 months of use than healthy controls (n=28). A prospective prevention study in postmenopausal women being at increased risk for BC reported no cognitive impairment in women taking anastrozole (n=79) compared to placebo (n=74) after 6 months and 2 years of therapy.

An explanation for potentially different effects on cognition between anastrozole and exemestane might be sought in the different pharmacological properties of both agents. Exemestane and its metabolites have mild androgenic properties, contrary to anastrozole. Because androgens might be beneficial for performance in several cognitive domains, detrimental effects on cognitive function of estrogen deprivation might be limited, or even prevented by the androgenic properties of exemestane. As the reported...
data for anastrozole are not congruent, it is important to obtain further data on this issue in studies in BC patients comparing different AIs directly with respect to their impact on cognition.

Our exploratory analyses of the younger (≤65 years) and older (>65 years) women separately showed larger effects, comprising more cognitive domains, in the older BC patients, suggesting a possible age-dependency of the effects of tamoxifen on cognition.

Despite the consistent finding of detrimental cognitive effects of tamoxifen in studies conducted until now, including this study, the mechanisms of action of tamoxifen on the brain are insufficiently known. Potential mechanisms to evaluate in future research should include the effects of tamoxifen on the two ERs, ERα and ERβ, in the brain. Since estrogens may have different effects on ERα and ERβ, which are also differentially expressed in various parts of the brain, this distinction might be relevant for tamoxifen as well. Additionally, tamoxifen may act as an antagonist and as an agonist of ERs, or via mechanisms that are independent of genomic actions. Finally, more research is needed to clarify the role of age with respect to the effects of tamoxifen on cognition.

The strengths of this study include the relatively large sample size compared to other neuropsychological studies in cancer patients, and the randomized allocation to either tamoxifen or exemestane resulting in very similar patient groups. Inclusion of baseline cognitive assessments made it possible to adjust for pre-existing cognitive differences between the groups. Furthermore, because none of the patients received chemotherapy, the results are not confounded by potential cognitive alterations induced by chemotherapy.

A limitation of our study is the relatively short observation period, covering 1 year of adjuvant endocrine treatment, while the recommended therapy duration at this moment is 5 years with the consideration of extended endocrine therapy in case of high risk BC. Another point of concern might be our finding of lower cognitive functioning of patients compared with healthy controls at T1. Cognitive problems before the start of systemic treatment are described in earlier studies. Although we have attempted to take the cognitive differences at T1 into account by means of a statistical adjustment, there is no
guarantee that such a statistical adjustment is sufficient to manage the differences completely.

In conclusion, our results suggest that compared to healthy controls, exemestane did not result in the same cognitive decline over time that was seen in BC patients taking tamoxifen. Although the impact of the observed cognitive effects on daily life of patients has yet to be determined, intact cognitive functioning is known to be an important precondition for independent living and wellbeing. In view of the already widespread and potentially even longer use of endocrine treatment for BC patients in the future, and the fact that the choice for a specific endocrine agent and therapy sequence among others is based on the safety profile, our results justify continuing research into the cognitive effects of endocrine therapy and stress the need for more detailed knowledge about differential effects of these therapies on neuropsychological functioning.

Acknowledgements

We thank all patients and healthy controls who participated in the study; the Datacenter Heelkunde of the Leiden University Medical Center for organizational support; M. Weevers, S. Leering and A. van Nuland for helping collecting the data; R. Michalides for his helpful comments; and physicians and research nurses of 38 Dutch hospitals for providing patients for this neuropsychological study. This original work was supported by an independent research grant from Pfizer, grant number 56850.
Chapter 5

Reference List


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Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: cross-sectional findings from the neuropsychological TEAM side study

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Abstract

Background. Previous studies have indicated that a subset of cancer patients treated with chemotherapy show cognitive deficits and/or experience cognitive complaints, whereas literature about the influence of hormonal therapies on cognition is sparse. Because of the accumulating knowledge about the importance of estrogen for cognitive functioning, there is growing concern about adjuvant hormonal therapy for breast cancer (BC) affecting cognition. We examined the cognitive functioning of postmenopausal BC patients who were, following doxorubicin/cyclophosphamide (AC) chemotherapy, randomized to tamoxifen or exemestane, and compared their performance with that of non-cancer controls.

Materials and Methods. Thirty BC patients using tamoxifen and 50 patients using exemestane underwent interviews, questionnaires and cognitive tests, on average two years after completion of AC chemotherapy. Forty eight healthy controls were tested with similar measures.

Results. Memory complaints were reported by 28% of AC/tamoxifen users, 24% of AC/exemestane users and 6% of healthy controls (p=0.02). Cognitive testing revealed no statistically significant differences between tamoxifen and exemestane users, but suggested that tamoxifen use is possibly related to worse verbal functioning, while exemestane use is possibly related to slower manual motor speed. Both patient groups performed significantly worse than healthy controls on verbal fluency and information processing speed.

Discussion. Our findings show that sequential treatment of AC-chemotherapy and hormonal therapy in postmenopausal, primary BC is associated with lower test scores for certain cognitive functions, and provide indications for possibly distinctive associations for different types of hormonal treatment. Future research with larger groups is recommended to obtain a more definite picture.
Introduction

Since the first publication in which comprehensive neuropsychological testing has been used, the literature describing relationships between adjuvant cytotoxic regimens and cognitive functioning is accumulating rapidly. A recent meta-analysis using seven cross-sectional studies suggests small to medium cumulative effect-sizes across eight cognitive domains, with lower cognitive functioning for breast cancer (BC) patients compared to healthy controls.¹ In recent years, several prospective longitudinal studies are published, of which most, but not all, found subtle negative influences of chemotherapy on cognitive functioning in a subset of patients.² The etiology of cognitive impairment during and/or after chemotherapy remains unknown although a number of mechanisms, for example direct neurotoxic effects, oxidative stress and DNA damage, induced hormonal changes, immune dysregulation and/or release of cytokines, and blood clotting in small CNS vessels have been postulated. A number of possible confounding factors hereby exist although it is suggested that mood/emotional status, menopausal status, fatigue and physical functioning do not drive the relation between adjuvant chemotherapy and cognitive impairment.² These factors however, may, well be related to self-reported cognitive problems in daily life.³

A large proportion of patients treated with chemotherapy will receive anti-estrogenic hormonal therapy additionally, often for years. As a result of increasing knowledge about the possible effects of estrogens on the brain and cognitive functioning, it has been questioned whether and how adjuvant hormonal therapies for BC are affecting cognitive functions.⁴,⁵ Possibly beneficial effects of estrogens on brain function may be among others the result of estrogenic activity through estrogen receptors (ER) in brain regions that are important for cognitive functioning, effects on neurotransmitters, protection against ischemic damage and increased survival of brain cells.⁶ The widely used selective estrogen receptor modulator (SERM) tamoxifen exerts anti-estrogenic effects on BC cells that contain estrogen receptors by blocking this receptor, and therefore inhibiting the binding of estrogens. On other tissues, for example bone and endometrium, tamoxifen has also estrogenic activities. Whether tamoxifen has estrogenic or anti-estrogenic qualities on brain tissue is insufficiently known. Evidence for a detrimental effect of tamoxifen on memory has been reported in animal studies with mice.⁷ With respect to BC patients, cognitive impairment associated with tamoxifen use is not yet well distinguished from cognitive impairment associated with chemotherapy and conflicting results are
Further, the influence of tamoxifen on cognitive functioning when chemotherapy is not administered also is uncertain due to lack of a specific study hereon. Limited cognitive assessment was performed as part of a mailed questionnaire by Paganini-Hill & Clark. They found no clear differences in test performances between tamoxifen- and non-tamoxifen users, although more women who had used tamoxifen for five years or longer reported seeing their physician for memory problems than non-users. Further evidence for anti-estrogenic effects in the brain was found in a neuro-imaging study (using PET and MRI), whereby tamoxifen users showed widespread area’s of hypometabolism and a trend towards smaller right hippocampal volumes relative to non-users and estrogen users. Opposite results were found in a proton magnetic resonance spectroscopy study comparing brain metabolism in tamoxifen-users with estrogen-users and controls. In both tamoxifen and estrogen-users, lower concentrations of myo-inositol (a brain marker that is associated with brain damage) were found than in the controls, suggesting that tamoxifen and estrogen have similar (possibly protective) effects on brain functioning.

Over the recent years, aromatase inhibitors (AI) are increasingly used as adjuvant hormonal therapy by postmenopausal, hormone sensitive BC patients either as upfront treatment or after 2-3 years of tamoxifen. These agents (anastrozole, letrozole, exemestane) reduce the postmenopausal estrogen levels by nearly complete inhibition of the enzyme aromatase. Their effect on cognitive functioning is by now largely unknown. Only for anastrozole, preliminary data from two small studies have been published, showing impaired performance among anastrozole users with regard to verbal memory and information processing speed and verbal and visual memory.

The goals of the current cross-sectional study were: (1) to study differences in cognitive performance of postmenopausal BC patients, randomly assigned to tamoxifen and exemestane after adjuvant doxorubicin and cyclophosphamide (AC) chemotherapy. (2) to compare cognitive functioning of postmenopausal BC patients treated with AC-chemotherapy followed by hormonal therapy with cognitive functioning of a healthy control group of the same age-range.
Materials and methods

Participants & procedure

This cross-sectional study was conducted in the context of a larger, prospective neuropsychological study into the cognitive effects of hormonal therapy in postmenopausal BC patients. Participants of both the prospective as well as the present cross-sectional study are patients from the Tamoxifen and Exemestane Multinational Trial (TEAM trial, an open label, randomized multinational comparative trial of 5 years adjuvant therapy with exemestane versus 2.5 years with tamoxifen followed by exemestane for 2.5 years). In the prospective neuropsychological study, patients who were not qualified to receive chemotherapy participated. The present, cross-sectional study was conducted among patients of 13 Dutch community hospitals who received AC-chemotherapy before the start of hormonal therapy.

Inclusion criteria for the TEAM trial were: (1) histologically/cytologically confirmed adenocarcinoma of the breast followed by intended curative surgery; (2) tumor size > 3 cm, or any N+, or tumor size 1-3 cm and one of the following: - MAI >10, - grade 3 according to Bloom-Richardson, - any TNM stage BC considered to receive adjuvant hormonal therapy; (3) ER and/or PgR status positive; (4) being postmenopausal; (5) adequate hematological, renal and hepatic function and (6) an Eastern Cooperative Oncology Group (ECOG) performance of 0 or 1. Exclusion criteria were: (1) palliative treatment, inflammatory breast cancer, positive supraclavicular nodes or ulceration/infiltration of local skin metastasis; (2) evidence of distant metastases; (3) previous adjuvant hormonal treatment; (4) uncontrolled cardiac disease; (5) psychiatric disorders preventing proper informed consent; (6) concomitant malignancies or other significant malignancies within the past 5 years; (7) or other serious illnesses; (8) HRT use not stopped at least 4 weeks prior to randomization; (9) bilateral tumor; (10) neo-adjuvant chemotherapy. For the current neuropsychological side study additional inclusion criteria were: (1) free of CNS disease; (2) no signs of dementia according to a dementia screenings tool (7 minutes screen\textsuperscript{14}); (3) being fluent in Dutch; and (4) use of the originally assigned hormonal agent for at least six months. The population of the present study consisted of three groups: a group of BC patients who received tamoxifen after completion of AC-chemotherapy, a group who received exemestane after AC-chemotherapy and a healthy comparison group. At the time of investigation, being on average 2 years after completion of chemotherapy, all patients were clinically free of disease. A comparison group of
healthy women was derived from an existing group of female friends and relatives of the BC patients participating in the prospective neuropsychological study of the TEAM trial. The recruitment of healthy controls took place through invitation by the patients of the prospective study. Patients were asked to invite a female friend or relative of approximately the same age to participate in the study and provided us contact information of interested women. Inclusion criteria for controls were: postmenopausal status, no history of CNS or malignant disease and fluent in the Dutch language. From this healthy control group, persons out of the age- and IQ-ranges of the patients of the current study were selected. Written informed consent was obtained from all participants. The ethical committees of all participating hospitals approved the study. Cognitive testing was conducted by experienced and trained research assistants.

Measures

Self-reported cognitive functioning

All participants were interviewed concerning cognitive complaints in daily life, regarding memory, concentration, thinking and language. The frequency of reported problems was scored as a number on a 5-point Likert scale (0=never; 1=once in a while; 2=regularly; 3=often; 4=always). In addition, the women filled out the Cognitive Failures Questionnaire (CFQ), a 25 item questionnaire regarding cognitive failures in daily life. In this questionnaire, the frequency of common lapses with regard to memory and attention is rated on a 4-point scale, ranging from ‘never’ to ‘always’.

Health-related quality of life, anxiety/depression, fatigue, menopausal symptoms

Health related quality of life was assessed by means of the EORTC quality of life questionnaire (EORTC QLQ-C30), that incorporates functional scales and scales/items to assess symptoms and global quality of life. Anxiety/depression was assessed with the Hopkins Symptom Checklist-25 (HSCL). To assess fatigue, the multi-dimensional fatigue inventory (MFI-20) was included in the study, while menopausal symptoms were assessed by the Endocrine Subscale of the Functional Assessment of Cancer Therapy – Breast questionnaire (FACT-B ES).
Neuropsychological functioning in patients treated with tamoxifen or exemestane after AC-chemotherapy

Cognitive tests
A comprehensive test battery was designed to assess a broad range of eight specific cognitive domains, comprising 18 test indices (21-29) (see table 1). Besides these outcome-variables, the Dutch Adult Reading Test (30) was used as a measure of pre-morbid verbal intelligence. Also, a dementia-screening tool was included to detect participants with signs of beginning dementia (7-minutes screen (14)). The tests were selected for reliability, validity, sensitivity for effects of hormones and suitability for older age groups.

Data analysis
The Statistical Package for Social Sciences (SPSS) WINDOWS 15.0 was used for statistical analyses. The data from the questionnaires were converted to scores according to standard scoring rules. Differences in sociodemographic characteristics between groups were analyzed by means of Chi-square tests for contingency tables or univariate analysis of variance. Differences between groups in scales from questionnaires were determined by univariate analysis of variance (ANOVA). To compare overall cognitive functioning between tamoxifen and exemestane users (goal 1), we performed multivariate analysis of variance (MANOVA) across all 18 cognitive test variables. Follow-up univariate analyses of variance (ANOVA) were conducted to determine the differences between separate tests. Both the MANOVA as well as the ANOVA’s were adjusted for age, IQ and time since completion of chemotherapy. MANOVA and subsequent ANOVA’s, adjusted for age and IQ, were used to compare cognitive functioning between patients and healthy controls.

In addition to the comparison of mean test scores, we determined the proportion of cognitively impaired persons in both patient groups and the control group. Cognitive test scores were converted into Z-scores using the mean and standard deviation (SD) of the healthy controls. When necessary, transformations were made so that higher Z-scores represented better performance. We considered failure on a test if the score was two standard deviations below the mean of the healthy control group (28). An overall impairment score was calculated for each patient by counting all tests on which the patient was impaired. The fifth percentile of the overall impairment scores of the healthy controls was used as a cut-off score to distinguish between normal and impaired cognitive functioning (3). Differences in proportions were tested with logistic regressions. Although differences in age and IQ between the three groups were not statistically significant, we
chose to adjust for age and IQ in the analyses because age and IQ are strong predictors for test performance.

**Table 1. Summary of cognitive test measures and outcome variables**

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Cognitive tests</th>
<th>Outcome variable</th>
<th>Score range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td>Rey auditory verbal learning test(^{21}) (Dutch shortened version)</td>
<td>1. Total of 3 trials</td>
<td>0-45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Total for long delay trial</td>
<td>0-15</td>
</tr>
<tr>
<td>Visual memory</td>
<td>Wechsler Memory Scale revised – visual memory subtest(^{22}) Visual Association Test(^{23})</td>
<td>3. Immediate recall</td>
<td>0-41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Delayed recall</td>
<td>0-41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Total of 2 trials</td>
<td>0-24</td>
</tr>
<tr>
<td>Working memory</td>
<td>WAIS III Letter-number sequencing(^{24})</td>
<td>6. Total correct trials</td>
<td>0-21</td>
</tr>
<tr>
<td>Attention/</td>
<td>Stroop Card 1(^{25})</td>
<td>7. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td>concentration</td>
<td>Stroop Card 2(^{25})</td>
<td>8. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Trailmaking A(^{26})</td>
<td>9. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td>Mental Flexibility</td>
<td>Stroop Card 3(^{25})</td>
<td>10. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Trailmaking B(^{26})</td>
<td>11. Seconds to complete</td>
<td>0+</td>
</tr>
<tr>
<td>Speed of information</td>
<td>Fepsy Reaction times: (^{27})</td>
<td>12. Mean msec/30 trials</td>
<td>0+</td>
</tr>
<tr>
<td>processing</td>
<td>1. dominant hand</td>
<td>13. Mean msec/30 trials</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>2. non-dominant hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual motor speed</td>
<td>Fepsy Finger tapping: (^{27})</td>
<td>14. Mean score of 5 trials of 10 seconds</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>1. dominant hand</td>
<td>15. Mean score of 5 trials of 10 seconds</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>2. non-dominant hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Letter fluency (D,A,T)(^{29})</td>
<td>16. Total score of 3 letters/1 minute</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td>Category Fluency (Animals/professions)(^{28})</td>
<td>17. Total score animals/1 minute</td>
<td>0+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18. Total score professions/1 minute</td>
<td>0+</td>
</tr>
</tbody>
</table>

Associations between neuropsychological test performance and anxiety/depression, fatigue, menopausal symptoms, time since completion of chemotherapy and reported cognitive complaints in daily life were analyzed using Pearson’s correlation coefficients. For those analyses, we used the mean Z-score of all test indices as a measure of overall cognitive functioning. A two-sided \(P\) value less than 0.05 was required for statistical significance, but for the 18 cognitive outcome measures, we applied a Bonferroni correction to adjust for multiple comparisons, requiring a two-sided \(P\) value of less than .0028 for statistical significance. Effects-sizes were calculated with Cohen’s \(d\) and based on
the partial eta squared after adjustment for age, IQ and (for the comparisons between tamoxifen and exemestane users) time since chemotherapy.

Results

Patient enrollment

Ninety-six patients were eligible for the study, 34 receiving tamoxifen and 62 receiving exemestane. These group sizes were unbalanced because patients who were assigned to tamoxifen but after 2-2.5 years had switched to exemestane according to the TEAM protocol were not eligible anymore, while patients who were assigned to exemestane remained eligible after 2-2.5 years. Twelve percent of the tamoxifen users (n=4) and 16% of the exemestane users (n=10) declined to participate, one patient had too serious problems with word finding to participate in the study and one was excluded due to multiple sclerosis, eventually leaving 80 patients (30 tamoxifen; 50 exemestane) eligible for analysis. The decliners were slightly older than the participants (mean age 60.3 and 58.3 years respectively).

With regard to the healthy controls, no information was available on the number of approached controls by the patients. Of the healthy control women who provided contact information, none declined participation. Three participants in the healthy control group used some type of hormonal treatment (two used HRT, one used a progestin). One participant had two missing test scores; estimates on the base of age and IQ were imputed for that participant using an expectation-maximization (EM) algorithm. According to the 7-minute screen test, none of the participants had signs of a beginning dementia.

Sociodemographic characteristics

The two patient groups and the healthy control group were well balanced with respect to demographic and medical history variables. With regard to clinical variables, the two patient groups only differed significantly on time since chemotherapy, i.e. longer time for exemestane users (table 2).
### Table 2. Sociodemographic characteristics of patients and controls

<table>
<thead>
<tr>
<th></th>
<th>AC/Tam (n=30)</th>
<th>AC/Exe (n=50)</th>
<th>Controls (n=48)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (SD)</td>
<td>57.9 (3.9)</td>
<td>58.5 (5.4)</td>
<td>60.2 (5.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>range</td>
<td>49-65</td>
<td>48-71</td>
<td>49-71</td>
<td></td>
</tr>
<tr>
<td>Level of education; % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>20 (6)</td>
<td>12 (6)</td>
<td>13 (6)</td>
<td>0.46</td>
</tr>
<tr>
<td>Middle</td>
<td>67 (20)</td>
<td>68 (34)</td>
<td>58 (28)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>13 (4)</td>
<td>20 (10)</td>
<td>29 (14)</td>
<td></td>
</tr>
<tr>
<td>IQ estimate; mean (SD)</td>
<td>98.7 (13.7)</td>
<td>104.0 (17.6)</td>
<td>103.0 (15.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Current treatment for:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- high blood pressure; % (n)</td>
<td>13 (4)</td>
<td>22 (11)</td>
<td>25 (12)</td>
<td>0.46</td>
</tr>
<tr>
<td>- diabetes mellitus; % (n)</td>
<td>0 (0)</td>
<td>8 (4)</td>
<td>6 (3)</td>
<td>0.30</td>
</tr>
<tr>
<td>HRT use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- previous; % (n)</td>
<td>23 (7)</td>
<td>38 (19)</td>
<td>21 (10)</td>
<td>0.13</td>
</tr>
<tr>
<td>- current; % (n)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>- never; % (n)</td>
<td>77 (23)</td>
<td>62 (31)</td>
<td>75 (36)</td>
<td></td>
</tr>
<tr>
<td>Current use of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- anti-depressive medication; % (n)</td>
<td>7 (2)</td>
<td>6 (3)</td>
<td>0 (0)</td>
<td>0.21</td>
</tr>
<tr>
<td>- benzodiazepines; % (n)</td>
<td>20 (6)</td>
<td>18 (9)</td>
<td>8 (4)</td>
<td>0.27</td>
</tr>
<tr>
<td>- cholesterol lowering agents; % (n)</td>
<td>7 (2)</td>
<td>4 (2)</td>
<td>13 (6)</td>
<td>0.28</td>
</tr>
<tr>
<td>Mean time since completion of chemotherapy; years (SD)</td>
<td>1.9 (0.5)</td>
<td>2.4 (0.7)</td>
<td>-</td>
<td>0.002</td>
</tr>
<tr>
<td>Past radiotherapy; % (n)</td>
<td>83 (25)</td>
<td>80 (40)</td>
<td>-</td>
<td>0.78</td>
</tr>
</tbody>
</table>

AC/Tam = doxorubicin/cyclophosphamide chemotherapy followed by tamoxifen.
AC/Exe = doxorubicin/cyclophosphamide chemotherapy followed by exemestane.
SD = standard deviation.

**Self-reported complaints of cognitive functioning**

Significantly more patients than healthy controls reported having complaints about their daily memory functioning (patients: 25%; healthy controls: 6%), but the proportion of patients reporting memory complaints did not differ between patients receiving tamoxifen (28%) and exemestane (24%). Regarding complaints about concentration, thinking and language and the cognitive failures self-report scale (CFQ), there were no differences between the three groups (table 3).
Table 3. Self-reported cognitive problems in daily life

<table>
<thead>
<tr>
<th></th>
<th>AC/Tam (n=30)</th>
<th>AC/Exe (n=50)</th>
<th>Controls (n=48)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory(^a); % (n)</td>
<td>28 (8)(^b)</td>
<td>24 (12)</td>
<td>6 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Concentration(^a); % (n)</td>
<td>21 (6)(^b)</td>
<td>18 (9)</td>
<td>13 (6)</td>
<td>0.60</td>
</tr>
<tr>
<td>Thinking(^a); % (n)</td>
<td>7 (2)</td>
<td>6 (3)</td>
<td>2 (1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Language(^a); % (n)</td>
<td>17 (5)</td>
<td>10 (5)</td>
<td>2 (1)</td>
<td>0.34</td>
</tr>
<tr>
<td>CFQ(^c); mean (SD)</td>
<td>33.8 (9.3)</td>
<td>36.7 (11.2)</td>
<td>32.6 (7.6)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

AC/Tam = doxorubicin/cyclophosphamide chemotherapy followed by tamoxifen.
AC/Exe = doxorubicin/cyclophosphamide chemotherapy followed by exemestane.
SD = standard deviation.
\(^a\) Patients who rated the frequency of their cognitive problem as at least 2 (‘regularly’) in a distinct domain were considered as having a complaint.
\(^b\) n=29.
\(^c\) Range 0-100, higher scores means higher frequency of cognitive lapses in daily life.

**Health related quality of life, anxiety and depression, fatigue and menopausal symptoms**

For none of the EORTC QLQ-C30 subscales statistical significant differences between tamoxifen and exemestane users were observed (table 4). The comparison between the combined patient groups and healthy controls revealed significantly lower scores on the cognitive functioning scale for patients (P=<0.001, d=0.62). On the symptom scales, patients reported more fatigue (P=0.002, d=0.56) and sleep disturbances (P=0.006, d=0.50) than healthy controls. There were no differences between the three groups with regard to symptoms of anxiety and depression (HSCL). With regard to menopausal symptoms (FACT-B ES) patients reported more problems than healthy controls (P=0.001, d=0.60), particularly on the items ‘hot flashes’, ‘cold sweats’ and ‘night sweats’ (table 4a).

**Cognitive test performance**

Overall cognitive functioning was not significantly different between tamoxifen and exemestane users (MANOVA F=1.33; P=0.21). Subsequent univariate ANOVA’s did not reveal a significant difference for any of the 18 test scores (table 5, left side). Effect-sizes were, in general, small. Mean scores of exemestane users were generally slightly better (although not statistically significant) on tests with a language component (verbal memory tests, verbal fluency tests, Stroop-test) and slightly worse on several tests with a motor-speed component (tapping test and Trailmaking test) compared to tamoxifen users.
Comparison of overall cognitive functioning between the total patient group and the healthy control group showed worse cognitive functioning of patients (MANOVA F=2.80, P=0.001). Univariate ANOVA’s suggest that two category fluency tests (animals: P=0.001; d=0.60; professions: P=<0.001; d=0.80) and one information processing speed tests (non-dominant hand, P=0.002; d=0.56) discriminated best between patients and healthy controls (table 5, right side).

The proportions of persons that were classified as cognitively impaired according to the definition did not differ between groups (healthy controls: 4%, n=2; tamoxifen users: 3%, n=1; exemestane users: 6%, n=3, data not shown).

Relationships between cognitive functioning, self-reported cognitive complaints, anxiety, depression, fatigue, menopausal complaints and time since completion of chemotherapy

Self-reported frequency of cognitive lapses (CFQ) showed significant correlations with anxiety (r=0.35), depression (r=0.45), fatigue (r=0.55) and menopausal symptoms (r=0.35), but not with overall cognitive performance and time since completion of chemotherapy. Anxiety, depression, fatigue and menopausal symptoms were strongly intercorrelated (r varying from 0.56 to 0.68). Better overall cognitive performance was weakly related to less fatigue (r=0.23) and a longer time since completion of chemotherapy (r=0.22). In addition, weak correlations exist between time since completion of chemotherapy and anxiety (r=0.25), fatigue (r=0.27) and cognitive performance (r=0.22) (data not shown).
Table 4. Health related quality of life (EORTC QLQ-C30) Left side: AC/tamoxifen users versus AC/exemestane users; Right side: combined patient group versus healthy controls

<table>
<thead>
<tr>
<th>EORTC QLQ-C30 Function Scales&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AC/Tam (n=30) Mean (SD)</th>
<th>AC/Exe (n=50) Mean (SD)</th>
<th>P-value&lt;sup&gt;f&lt;/sup&gt;</th>
<th>Effect-size&lt;sup&gt;g&lt;/sup&gt;</th>
<th>Combined patient group (n=80) Mean (SD)</th>
<th>Controls (n=48) Mean (SD)</th>
<th>P-value</th>
<th>Effect-size&lt;sup&gt;g&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>83.8 (14.9)</td>
<td>86.7 (14.4)</td>
<td>0.54</td>
<td>0.14</td>
<td>85.6 (14.6)</td>
<td>87.2 (15.0)</td>
<td>0.54</td>
<td>0.11</td>
</tr>
<tr>
<td>Role</td>
<td>81.1 (23.0)</td>
<td>84.0 (23.6)</td>
<td>0.83</td>
<td>0.05</td>
<td>82.9 (23.3)</td>
<td>89.9 (19.7)</td>
<td>0.08</td>
<td>0.31</td>
</tr>
<tr>
<td>Cognitive</td>
<td>79.4 (23.0)</td>
<td>80.3 (20.9)</td>
<td>0.86</td>
<td>0.04</td>
<td>80.0 (21.6)</td>
<td>92.0 (12.9)</td>
<td>0.001</td>
<td>0.62</td>
</tr>
<tr>
<td>Emotional</td>
<td>84.7 (20.2)</td>
<td>84.3 (15.8)</td>
<td>0.74</td>
<td>0.08</td>
<td>84.5 (17.4)</td>
<td>85.8 (17.2)</td>
<td>0.69</td>
<td>0.07</td>
</tr>
<tr>
<td>Social</td>
<td>91.7 (21.3)</td>
<td>89.3 (18.1)</td>
<td>0.56</td>
<td>0.13</td>
<td>90.2 (19.2)</td>
<td>93.4 (14.9)</td>
<td>0.33</td>
<td>0.18</td>
</tr>
<tr>
<td>Global QoL</td>
<td>79.2 (17.6)</td>
<td>81.2 (17.2)</td>
<td>0.99</td>
<td>0.00</td>
<td>80.4 (17.3)</td>
<td>85.2 (16.7)</td>
<td>0.12</td>
<td>0.28</td>
</tr>
<tr>
<td>EORTC QLQ-C30 Symptom scales&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Fatigue</td>
<td>28.5 (20.6)</td>
<td>23.8 (21.4)</td>
<td>0.55</td>
<td>0.14</td>
<td>25.6 (21.1)</td>
<td>15.0 (12.7)</td>
<td>0.002</td>
<td>0.56</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>6.1 (18.8)</td>
<td>3.3 (8.2)</td>
<td>0.56</td>
<td>0.13</td>
<td>4.4 (13.2)</td>
<td>1.4 (4.7)</td>
<td>0.13</td>
<td>0.27</td>
</tr>
<tr>
<td>Pain</td>
<td>22.2 (27.8)</td>
<td>18.3 (24.6)</td>
<td>0.81</td>
<td>0.05</td>
<td>19.8 (25.7)</td>
<td>19.1 (27.5)</td>
<td>0.89</td>
<td>0.03</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16.7 (21.0)</td>
<td>6.7 (16.5)</td>
<td>0.05</td>
<td>0.45</td>
<td>10.4 (18.8)</td>
<td>6.3 (14.8)</td>
<td>0.19</td>
<td>0.23</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>37.8 (31.2)</td>
<td>31.3 (31.2)</td>
<td>0.38</td>
<td>0.20</td>
<td>33.8 (31.1)</td>
<td>18.9 (26.5)</td>
<td>0.006</td>
<td>0.50</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>8.9 (19.4)</td>
<td>6.0 (17.4)</td>
<td>0.46</td>
<td>0.17</td>
<td>7.1 (18.1)</td>
<td>4.2 (16.3)</td>
<td>0.36</td>
<td>0.16</td>
</tr>
<tr>
<td>Constipation</td>
<td>4.4 (14.5)</td>
<td>7.3 (15.5)</td>
<td>0.27</td>
<td>0.25</td>
<td>6.3 (15.1)</td>
<td>4.2 (11.1)</td>
<td>0.41</td>
<td>0.15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.2 (8.5)</td>
<td>3.3 (15.4)</td>
<td>0.36</td>
<td>0.21</td>
<td>2.9 (13.2)</td>
<td>2.1 (8.2)</td>
<td>0.69</td>
<td>0.07</td>
</tr>
<tr>
<td>Financial impact</td>
<td>2.2 (8.5)</td>
<td>4.0 (12.8)</td>
<td>0.27</td>
<td>0.26</td>
<td>3.3 (11.3)</td>
<td>1.4 (6.7)</td>
<td>0.28</td>
<td>0.19</td>
</tr>
</tbody>
</table>

AC/Tam = doxorubicin/cyclophosphamide chemotherapy followed by tamoxifen.
AC/Exe = doxorubicin/cyclophosphamide chemotherapy followed by exemestane.
SD = standard deviation.
EORTC = European Organization for Research on Treatment of Cancer; EORTC QLQ-C30 is a health-related quality of life questionnaire (see ‘Materials and methods’ section for more details).

<sup>a</sup> Higher scale means better functioning; scale 0-100.

<sup>b</sup> Higher score means more serious complaints; scale 0-100.

<sup>f</sup> P-value adjusted for time since completion of chemotherapy.

<sup>g</sup> Cohen’s $d$: <0.20: small effect, 0.20-0.80: medium effect, >0.80: large effect.
Table 4a. Anxiety and Depression (HSCL), Fatigue (MFI) and Menopausal symptoms (FACT-B ES). Left side: AC/tamoxifen users versus AC/exemestane users; Right side: combined patient group versus healthy controls

<table>
<thead>
<tr>
<th></th>
<th>AC/Tam (n=30) Mean (SD)</th>
<th>AC/Exe (n=50) Mean (SD)</th>
<th>P-value(^f)</th>
<th>Effect-size(^g)</th>
<th>Combined patient group (n=80) Mean (SD)</th>
<th>Controls (n=48) Mean (SD)</th>
<th>P-value(^f)</th>
<th>Effect-size(^g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HSCL</strong>(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>14.7 (9.0)</td>
<td>10.2 (9.9)</td>
<td>0.20</td>
<td>0.29</td>
<td>11.9 (9.87)</td>
<td>9.9 (11.0)</td>
<td>0.28</td>
<td>0.19</td>
</tr>
<tr>
<td>Depression</td>
<td>13.5 (9.9)</td>
<td>13.1 (9.9)</td>
<td>0.81</td>
<td>0.06</td>
<td>13.2 (9.8)</td>
<td>9.8 (10.8)</td>
<td>0.07</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>MFI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General fatigue(^c)</td>
<td>10.6 (4.1)</td>
<td>9.2 (3.9)</td>
<td>0.38</td>
<td>0.20</td>
<td>9.7 (4.0)</td>
<td>7.6 (3.1)</td>
<td>0.002</td>
<td>0.56</td>
</tr>
<tr>
<td>Physical fatigue(^c)</td>
<td>9.6 (4.7)</td>
<td>8.7 (4.1)</td>
<td>0.97</td>
<td>0.01</td>
<td>9.0 (4.3)</td>
<td>7.9 (3.5)</td>
<td>0.12</td>
<td>0.28</td>
</tr>
<tr>
<td>Reduction of activities(^c)</td>
<td>9.2 (4.5)</td>
<td>9.2 (4.1)</td>
<td>0.46</td>
<td>0.17</td>
<td>9.2 (4.2)</td>
<td>7.3 (2.9)</td>
<td>0.006</td>
<td>0.49</td>
</tr>
<tr>
<td>Reduction of motivation(^c)</td>
<td>8.8 (3.4)</td>
<td>7.9 (3.4)</td>
<td>0.56</td>
<td>0.13</td>
<td>8.3 (3.4)</td>
<td>6.5 (3.0)</td>
<td>0.004</td>
<td>0.52</td>
</tr>
<tr>
<td>Mental fatigue(^c)</td>
<td>10.5 (4.1)</td>
<td>9.7 (4.5)</td>
<td>0.85</td>
<td>0.04</td>
<td>10.0 (4.3)</td>
<td>8.7 (3.8)</td>
<td>0.10</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>FACT-B ES total score(^d)</strong></td>
<td>57.7 (8.2)</td>
<td>57.0 (9.1)</td>
<td>0.38</td>
<td>0.20</td>
<td>57.3 (8.7)</td>
<td>62.1 (6.1)</td>
<td>0.001</td>
<td>0.60</td>
</tr>
</tbody>
</table>

\(^{AC/Tam} = doxorubicin/cyclophosphamide chemotherapy followed by tamoxifen.\)

\(^{AC/Exe} = doxorubicin/cyclophosphamide chemotherapy followed by exemestane.\)

\(^{SD} = standard deviation.\)

\(^{HSCL} (Hopkins Symptom Check-list-25) is an anxiety/depression symptom checklist; MFI (multi-dimensional fatigue inventory) is a questionnaire addressing several dimensions of fatigue, FACT-B ES (Endocrine Subscale of the Functional Assessment of Cancer Therapy – Breast questionnaire) is a questionnaire for assessment of menopausal symptoms (see ‘Materials and methods’ section for more details).\)

\(^{b} Higher score means more serious complaints; scale 0-100.\)

\(^{c} Higher score means more serious complaints; scale 4-20.\)

\(^{d} Higher score means less serious complaints; scale 0-72.\)

\(^{f} P-value adjusted for time since completion of chemotherapy.\)

\(^{g} Cohen's \(d\): <0.20: small effect, 0.20-0.80: medium effect, >0.80: large effect.\)
### Table 5. Raw cognitive test scores. Left side: AC/tamoxifen users versus AC/exemestane users; Right side: combined patient group versus controls

<table>
<thead>
<tr>
<th>Cognitive domains and tests (see table 1 for more details)</th>
<th>AC/Tam (^a) (n=30) Mean (SD)</th>
<th>AC/Exe (^b) (n=50) Mean (SD)</th>
<th>P-value(^c)</th>
<th>Effect-size(^g)</th>
<th>Patients, combined (^n=80) Mean (SD)</th>
<th>Controls (n=48) Mean (SD)</th>
<th>P-value(^d)</th>
<th>Effect-size(^l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>RAVLT immediate(^e)</td>
<td>21.2 (5.1)</td>
<td>22.8 (4.7)</td>
<td>0.22</td>
<td>0.29</td>
<td>22.2 (4.9)</td>
<td>23.5 (5.2)</td>
<td>0.08</td>
<td>0.31</td>
</tr>
<tr>
<td>RAVLT delayed(^f)</td>
<td>6.6 (2.2)</td>
<td>7.0 (2.2)</td>
<td>0.42</td>
<td>0.19</td>
<td>6.8 (2.2)</td>
<td>7.3 (2.9)</td>
<td>0.21</td>
<td>0.22</td>
</tr>
<tr>
<td>Visual memory</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Visual Association Test(^f)</td>
<td>20.5 (2.9)</td>
<td>21.5 (2.3)</td>
<td>0.16</td>
<td>0.33</td>
<td>21.1 (2.5)</td>
<td>21.3 (2.4)</td>
<td>0.54</td>
<td>0.11</td>
</tr>
<tr>
<td>WMS Visual memory immediate(^f)</td>
<td>32.9 (5.8)</td>
<td>32.6 (4.7)</td>
<td>0.57</td>
<td>0.13</td>
<td>32.7 (5.1)</td>
<td>33.6 (4.4)</td>
<td>0.16</td>
<td>0.25</td>
</tr>
<tr>
<td>WMS Visual memory delayed(^f)</td>
<td>29.4 (7.3)</td>
<td>29.2 (6.8)</td>
<td>0.36</td>
<td>0.21</td>
<td>29.3 (7.0)</td>
<td>30.7 (5.3)</td>
<td>0.10</td>
<td>0.30</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter Number Sequencing(^f)</td>
<td>9.7 (2.1)</td>
<td>10.1 (2.4)</td>
<td>0.64</td>
<td>0.11</td>
<td>9.9 (2.3)</td>
<td>9.8 (2.4)</td>
<td>0.79</td>
<td>0.05</td>
</tr>
<tr>
<td>Attention/Concentration</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Stroop Card (^g)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Stroop Card 1(^g)</td>
<td>48.7 (8.1)</td>
<td>44.8 (6.1)</td>
<td>0.13</td>
<td>0.36</td>
<td>46.3 (7.2)</td>
<td>46.1 (7.5)</td>
<td>0.86</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroop Card 2(^g)</td>
<td>62.2 (9.9)</td>
<td>58.1 (9.0)</td>
<td>0.16</td>
<td>0.33</td>
<td>60.0 (9.5)</td>
<td>60.1 (9.6)</td>
<td>0.97</td>
<td>0.01</td>
</tr>
<tr>
<td>Trailmaking A(^g)</td>
<td>36.5 (13.8)</td>
<td>40.3 (16.4)</td>
<td>0.07</td>
<td>0.43</td>
<td>38.9 (15.5)</td>
<td>36.0 (10.5)</td>
<td>0.12</td>
<td>0.28</td>
</tr>
<tr>
<td>Mental flexibility</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Stroop Card 3(^g)</td>
<td>108.7 (22.0)</td>
<td>97.7 (22.5)</td>
<td>0.07</td>
<td>0.42</td>
<td>101.8 (22.8)</td>
<td>96.4 (18.2)</td>
<td>0.02</td>
<td>0.43</td>
</tr>
<tr>
<td>Trailmaking B(^g)</td>
<td>82.6 (25.2)</td>
<td>86.8 (35.3)</td>
<td>0.08</td>
<td>0.40</td>
<td>85.2 (31.8)</td>
<td>82.1 (31.7)</td>
<td>0.21</td>
<td>0.23</td>
</tr>
<tr>
<td>Information Processing Speed</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT – dominant hand(^h)</td>
<td>355 (84)</td>
<td>339 (66)</td>
<td>0.62</td>
<td>0.12</td>
<td>345 (73)</td>
<td>316 (47)</td>
<td>0.01</td>
<td>0.47</td>
</tr>
<tr>
<td>RT – non-dominant hand(^h)</td>
<td>340 (98)</td>
<td>347 (68)</td>
<td>0.74</td>
<td>0.08</td>
<td>344 (80)</td>
<td>304 (53)</td>
<td>0.002</td>
<td>0.56</td>
</tr>
<tr>
<td>Motor Speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapping dominant hand(^i)</td>
<td>60.2 (8.3)</td>
<td>59.0 (8.4)</td>
<td>0.24</td>
<td>0.28</td>
<td>59.4 (8.3)</td>
<td>54.9 (8.2)</td>
<td>0.01</td>
<td>0.45</td>
</tr>
<tr>
<td>Tapping non-dominant hand(^i)</td>
<td>53.9 (7.5)</td>
<td>53.2 (7.8)</td>
<td>0.50</td>
<td>0.16</td>
<td>53.4 (7.7)</td>
<td>50.4 (7.3)</td>
<td>0.06</td>
<td>0.34</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category fluency animals(^j)</td>
<td>21.4 (4.1)</td>
<td>23.0 (5.6)</td>
<td>0.42</td>
<td>0.19</td>
<td>22.4 (5.2)</td>
<td>25.5 (6.3)</td>
<td>0.001</td>
<td>0.60</td>
</tr>
<tr>
<td>Category fluency professions(^j)</td>
<td>16.6 (4.0)</td>
<td>17.4 (4.6)</td>
<td>0.66</td>
<td>0.10</td>
<td>17.1 (4.4)</td>
<td>20.9 (6.0)</td>
<td>&lt;.001</td>
<td>0.80</td>
</tr>
<tr>
<td>Letter fluency (DAT)(^k)</td>
<td>33.5 (9.3)</td>
<td>39.0 (10.9)</td>
<td>0.14</td>
<td>0.34</td>
<td>36.9 (10.7)</td>
<td>39.5 (11.9)</td>
<td>0.14</td>
<td>0.27</td>
</tr>
</tbody>
</table>

\(^a\)AC/Tam = doxorubicin/cyclophosphamide (AC) chemotherapy followed by tamoxifen; \(^b\)AC/Exe = AC chemotherapy followed by exemestane; SD = standard deviation; \(^c\)adjusted for age/IQ/time since completion chemotherapy; \(^d\)adjusted for age/IQ; \(^e\)total number of words after 3 trials; \(^f\)number of correct responses; \(^g\)seconds to complete task (lower scores represent better performance); \(^h\)milliseconds (lower scores represent better performance); \(^i\)mean of 5 trials of 10 seconds; \(^j\)total of words produced in 1 minute; \(^k\)total number of words produced in 3 minutes (1 minute for each letter). \(^l\)Cohen's \(d\): <0.20: small effect, 0.20-.80: medium effect, >0.80: large effect.
Discussion

There is growing evidence for cognitive dysfunction during and/or after adjuvant systemic treatment for BC, but associations between different hormonal treatments and cognitive functioning have not yet been thoroughly studied. The present study does not reveal clear differences in cognitive performance between tamoxifen and exemestane users after exposure to AC-chemotherapy. However, exploratory analyses suggest that for most tests with a verbal component (verbal memory, verbal fluency, Stroop test) exemestane users outperformed tamoxifen users, while for several tests with a manual motor-speed component (tapping, Trailmaking test) tamoxifen users performed better than exemestane users. Although speculative because of the small and non-significant differences, an explanation could be that tamoxifen and exemestane potentially have distinctive effects on different cognitive domains. Distinctive effects between tamoxifen and aromatase inhibitors are theoretically possible given the different mechanisms of action, but this issue is hardly studied until now. Only one, very small study reported on distinctive effects of tamoxifen and anastrozole, suggesting poorer verbal and visual memory for anastrozole users. From our data, a different picture arises, suggesting that tamoxifen is associated with worse verbal functioning while exemestane negatively is associated with worse manual motor speed. Because a negative impact on musculoskeletal function has been described for aromatase inhibitors, it is possible that motor speed-deficits in exemestane users are rather a musculoskeletal feature than a cognitive problem. So, this should be taken into account in further cognitive studies.

While clear differences in cognitive functioning between tamoxifen users and exemestane users were lacking in our patient groups, differences between the combined patient group and healthy controls were present. Treatment with AC-chemotherapy followed by hormonal therapy is associated with a lower level of cognitive performance. The cognitive domains that show significant differences are verbal fluency and information processing speed. These findings are consistent with earlier studies, although deficits in other domains (for example visual memory) also have been described. A remarkable finding in this analysis is that, although mean scores of several tests differ between the groups, we did not observe differences in the proportions of cognitively impaired persons. This suggests that the combination of AC-chemotherapy and hormonal therapy is related to subtle cognitive impairment in a substantial part of the patients instead of substantial cognitive impairment in a small subgroup of patients. This finding differs from earlier
Neuropsychological functioning in patients treated with tamoxifen or exemestane after AC-chemotherapy

studies that often showed clear differences in proportions of impaired patients while differences in mean test scores are rather small.\textsuperscript{15}

Because we made use of a healthy, non-cancer control group, it is possible that being diagnosed as a cancer patient, or surgical and/or radiotherapeutic procedures influence cognitive performance of the patients. An earlier study showed that a breast cancer control group who did receive radiotherapy but no systemic treatment did not score different from published test norms and concluded that it is unlikely that cognitive impairment is a consequence of these factors.\textsuperscript{15} Nevertheless, due to the cross-sectional nature of the study, we can not rule out the possibility that pre-treatment differences between the patients and the healthy controls have influenced the differences in cognitive performance found.

With respect to self-reported cognitive functioning, our study shows, which is consistent with previous studies\textsuperscript{3} that a higher proportion of treated patients experienced memory problems in daily life compared to healthy controls. The proportion was not different between tamoxifen and exemestane users. Self-reported cognitive functioning in our data is, consistent with previous data\textsuperscript{3,8}, related to anxiety, depression and fatigue, but not with cognitive test performance. Furthermore, cognitive test performance is not related to anxiety and depression. Strengths of this study are the randomized attribution of the hormonal agents and the homogeneity with regard to the used chemotherapy regimen. Furthermore, inclusion of a control group enabled us to consider cognitive performance, psychological functioning and quality of life data of BC patients within the perspective of daily functioning of healthy postmenopausal women.

However, our study also has several limitations. First, the sample sizes of each of the groups are relatively small and unbalanced, and second, the patient groups differed with respect to time since completion of chemotherapy. These differences were particularly a result of our inclusion criteria: patients allocated to tamoxifen treatment were not eligible after their switch to exemestane, while patients allocated to exemestane were eligible irrespective of time on treatment. The difference in time since chemotherapy might be of influence on cognitive performance. However, it is unclear in what direction this influence would be, and for which treatment group this might be beneficial. A longer time since chemotherapy means also a longer time since diagnosis and surgery, but also a longer
time on hormonal treatment and a longer survival time. Because we did not know to what extent and in which direction these differences might influence our results, we considered ‘time since completion of chemotherapy’ as a confounder and adjusted for it in all comparisons between the two patient groups. Third, because of the cross-sectional nature of the study, corrections for pre-treatment differences between the groups could not be made, changes in cognitive function over time could not be studied and causal relationships between treatments and cognitive functioning could not be established. Forth, our study did not include a patient group treated with only AC-chemotherapy and no hormonal therapy. Therefore, it was not possible to distinguish between the effects of AC-chemotherapy and the effects of hormonal therapy. From the literature, data on the specific cognitive sequelae after standard dosed AC-chemotherapy in postmenopausal BC patients are not available either.

Our study provides additional data supporting the fact that systemic therapy for BC is associated with subtle cognitive impairment in postmenopausal patients, although our data does not give evidence for a particular subgroup of patients with outlying test scores. Of interest, our study suggests that tamoxifen and exemestane potentially exert distinctive effects on cognitive functioning, maybe related to different mechanisms of action, i.e. anti-estrogenic as well as estrogenic effects for tamoxifen versus blocking of estrogen production for exemestane. To unravel the separate effects of chemotherapy and hormonal therapy, and to establish causal relationships between these systemic treatment and cognitive functioning, larger prospective neuropsychological studies are needed in patients who are qualified to receive hormonal therapy only, and patients who are qualified to receive chemotherapy only.

Acknowledgements
We are indebted to all patients, healthy controls as well as physicians and research nurses of 13 Dutch hospitals that participated in this cognitive study. We are also grateful to M. Weevers, S. Leering and A. van Nuland for helping collecting the data. This original work was supported by an independent research grant from Pfizer, grant number 56850.
Neuropsychological functioning in patients treated with tamoxifen or exemestane after AC-chemotherapy

Reference List


Self-reported cognitive functioning in postmenopausal breast cancer patients before and during endocrine treatment: findings from the neuropsychological TEAM side study

Christina M Schilder, Caroline Seynaeve, Sabine C Linn, Willem Boogerd, Louk V Beex, Chad M Gundy, Johan W Nortier, Cornelis J van de Velde, Frits S van Dam, Sanne B Schagen. Submitted
Abstract

Objective: This study aims (1) to evaluate self-reported cognitive functioning of postmenopausal breast cancer patients before and during endocrine treatment, compared to healthy female controls, and (2) to investigate associations between self-reported cognitive functioning, cognitive test performance and anxiety/depression, fatigue and menopausal complaints.

Methods: Self-reported cognitive functioning, anxiety/depression, fatigue, menopausal complaints and cognitive tests performance were assessed before (T1) and after one year (T2) of adjuvant endocrine treatment in postmenopausal chemotherapy-naïve breast cancer patients (n=179). Patients participated in the TEAM trial, a prospective randomized study investigating tamoxifen versus exemestane as adjuvant therapy for hormone-sensitive breast cancer. Identical information was obtained from healthy postmenopausal volunteers (n=120).

Results: At T1, the three groups did not differ significantly with regard to the prevalence of self-reported cognitive complaints. At T2, adjusted for complaints at T1, the prevalence of concentration, but not of memory complaints differed significantly between the groups, due to increased concentration complaints among tamoxifen users. The self-reported frequency of cognitive failures did not change over time in patients and healthy controls. Cognitive test performance was not associated with self-reported cognitive functioning, but weakly with anxiety/depression and fatigue. Self-reported cognitive functioning showed moderate associations with anxiety/depression, fatigue and menopausal complaints.

Conclusion: Adjuvant therapy with tamoxifen is associated with a higher prevalence of self-reported concentration complaints. This association was not observed in exemestane users. In both patient groups the self-reported frequency of cognitive failures did not change over time. Cognitive complaints can not be regarded as substitutes for cognitive test performance.
Introduction

Cognitive complaints, such as memory and concentration problems, are frequently reported by breast cancer patients before, during and after adjuvant (systemic) treatment. Available data from studies investigating cognitive functioning in breast cancer patients describe that 21-90% of patients report cognitive complaints.\(^1\)\(^-\)\(^5\) The wide variation in so-called patient reported outcomes (pro’s) of cognitive functioning is due to differences in instruments and definitions. Whether the observed proportions are higher in breast cancer patients than in the general population is unclear.\(^3\) In healthy populations of a broad age-range, cognitive complaints are raised with an estimated prevalence varying between 25-50\%.\(^6\)\(^,\)\(^7\)

Self-reported cognitive complaints have been interpreted as a reflection of cognitive capacity\(^8\), although it is known that individual self-reports do not necessarily correspond with actual cognitive ability as assessed by means of neuropsychological tests.\(^6\) Associations between self-reported cognitive functioning and cognitive test performance have been investigated in cancer patients\(^1\)\(^,\)\(^5\)\(^-\)\(^11\), but also in patients with other disorders, for example multiple sclerosis\(^12\), head injury\(^13\), epilepsy\(^14\), ecstasy use\(^15\) as well as in healthy older adults.\(^16\)\(^-\)\(^18\) Independent of the population, associations were found to be weak, or even absent. In a recent review by Pullens et al.\(^3\) strong evidence was found for a lack of correlation between self-reported cognitive functioning and cognitive test performance in cancer patients.

The lack of associations between self-reported cognitive functioning and cognitive test performance is a complex issue in neuropsychology. In the literature, multiple explanations are postulated such as low correspondence of the cognitive tests with ‘real world’ cognitive functioning (ecological validity)\(^1\) and shortcomings in the instruments used to measure self-reported cognitive functioning.\(^19\) Additionally, associations may be weak because self-reported cognitive functioning and test performance are influenced by distinctive factors. Described predictors for self-reported cognitive functioning are among others personality characteristics\(^20\), anxiety/depression\(^17\), fatigue\(^21\), individual believes about the own cognitive ability in different situations\(^22\) and the requirements of the professional and social situation relative to the cognitive capacities.\(^23\) In contrast, the level of someone’s cognitive test performance is largely determined by factors such as education, IQ, age, aptitudes and previous training.\(^24\) Therefore, it is possible and
understandable that two persons with the same level of cognitive performance will judge their cognitive functioning differently, thereby reducing the strength of the correlations.

In view of the growing understanding of the role of estrogens in cognitive functioning, and the resulting concerns about the possible cognitive effects of endocrine treatments in breast cancer patients, we prospectively evaluated the influence of the selective estrogen receptor modulator (SERM) tamoxifen and the aromatase inhibitor (AI) exemestane on self-reported cognitive functioning and cognitive test performance of postmenopausal breast cancer patients. The current study was conducted in Dutch women participating in the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial\textsuperscript{25}, a prospective randomized study investigating tamoxifen versus exemestane as adjuvant therapy for hormone-sensitive, postmenopausal breast cancer. Detailed results regarding cognitive test performance have been described elsewhere.\textsuperscript{26} In short, after one year of adjuvant therapy, tamoxifen use was associated with significantly lower functioning in verbal memory and executive functioning, while exemestane use was not associated with any significantly lower cognitive functioning. The results with respect to tamoxifen are in line with other cognitive functioning studies\textsuperscript{11,27,28}, whereas there are no previously reported data of the impact of exemestane on cognitive functioning to compare with. Little information is available about cognitive functioning that is \textit{self-reported} by users of endocrine treatment.

The first aim of the present analysis was to evaluate \textit{self-reported} cognitive functioning of postmenopausal breast cancer patients both before and during endocrine treatment in comparison with healthy female controls of approximately the same age. The second aim was to explore associations between self-reported cognitive functioning, cognitive test performance and anxiety/depression, fatigue and menopausal complaints in the total study population. Knowledge about these associations is important in order to inform patients adequately and to determine possible further diagnostics and treatment.

\textbf{Patients and Methods}

\textit{Study population}

Eligible patients were Dutch postmenopausal women participating in the TEAM trial; an international, open label, randomized study comparing the efficacy and safety of 5 years
Self-reported cognitive functioning before and during endocrine treatment

of adjuvant exemestane (25 mg/day) with 2,5 years of tamoxifen (20 mg/day) followed by
2,5 years of exemestane in early, hormone-sensitive breast cancer. Extended data on in-
and exclusion criteria of the TEAM trial have been described previously. In short, eligible
patients were postmenopausal with histologically confirmed, estrogen receptor (ER)-
and/or progesterone receptor (PR)-positive adenocarcinoma of the breast, locally treated
with curative intent and candidates for adjuvant endocrine therapy. Because the
neuropsychological side study focused on the cognitive effects of endocrine therapy only
patients who were not scheduled to receive chemotherapy were eligible. Additional
exclusion criteria were: Central Nervous System (CNS) disease, not being fluent in Dutch
and signs of dementia according to a dementia screenings tool (7-minutes screen). The
study was approved by the central review board of the Erasmus MC, Rotterdam, and the
local medical ethic committees of all participating hospitals. The control group consisted
of healthy female friends or family members of the participating TEAM patients of
approximately the same age. Inclusion criteria for controls were: postmenopausal status,
no history of CNS disease or malignant disease, fluent in the Dutch language and no signs
of dementia according to the dementia screenings tool. All participants provided written
informed consent.

Participants underwent the neuropsychological assessments twice: after surgery, but
before the start of endocrine treatment (T1) and after one year of endocrine treatment
(T2). Healthy controls also were assessed twice with an interval of approximately one
year.

Measures: Patient reported outcome measures (pro’s) regarding cognitive functioning,
anxiety/depression, fatigue and menopausal complaints

Two self-report instruments were used to measure two distinct aspects of self-reported
cognitive functioning. First, an interview was performed to evaluate the prevalence of
current cognitive complaints. Participants were asked two general questions: (“do you
have complaints with regard to memory?”(yes/no) and “do you have complaints with
regard to concentration?”(yes/no)). In addition, the presence or absence of several often
by cancer patients mentioned memory problems (forgetting appointments, losing one’s
things and forgetting telephone numbers) and concentration problems (distractibility,
problems with sustained attention and problems with multitasking) was assessed
(yes/no). The questions were taken from a structured interview that is frequently used in cancer populations and were originally derived from a Dutch depression and anxiety questionnaire.\textsuperscript{[10,31,32]} Secondly, the \textit{frequency of everyday cognitive failures} was evaluated by means of the Cognitive Failures Questionnaire (CFQ, Dutch version). The CFQ consists of 25 items measuring the frequency of cognitive failures concerning memory, attention, motor function and perception. Each item is rated for frequency, from 4 (‘very often’) to 0 (‘never’). The psychometric qualities of this questionnaire are satisfactory.\textsuperscript{[33,34]}

For measuring symptoms of anxiety/depression the Hopkins Symptom Checklist (HSCL-25) was used. The HSCL-25 consists of 15 depression and 10 anxiety items, rated on a 4-point severity scale (ranging from ‘not at all’ to ‘very serious’) and was especially developed for ease and appropriateness in medical settings. The HSCL has been found to be a psychometrically valid and reliable indicator of anxiety and depression symptoms.\textsuperscript{35} or fatigue the 3-item fatigue subscale of the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) was used. This subscale has shown to be a reliable and valid measure of fatigue in clinical research settings.\textsuperscript{36} The items are rated on a 4-point severity scale ranging from ‘not at all’ to ‘very serious’. Menopausal complaints were assessed by the 18-item Endocrine Subscale of the Functional Assessment of Cancer Therapy–Breast questionnaire (FACT-B ES), a reliable and valid questionnaire that is sensitive to clinically significant change.\textsuperscript{37} The items are rated on a 5-point severity scale ranging from ‘not at all’ to ‘very serious’. For the EORTC QLQ-C30 fatigue scale and the HSCL, the timeframe of evaluation was the past week, for the FACT-B ES the past month. The interview questions and the CFQ referred to the current frequency of cognitive complaints and cognitive failures.

\textit{Cognitive tests}

Cognitive functioning was assessed by a comprehensive test battery, existing of 18 test indices covering the cognitive domains of \textit{verbal memory} (Rey auditory verbal memory test: immediate and delayed recall, Visual association test), \textit{visual memory} (WMS visual memory: immediate and delayed recall\textsuperscript{38}), \textit{information processing speed} (Trailmaking A\textsuperscript{39}, Stroop Card 1 and 2\textsuperscript{40}), \textit{executive functioning} (Trailmaking B\textsuperscript{39}, Stroop Card 3\textsuperscript{40}), \textit{working memory} (WAIS-III Letter-number sequencing\textsuperscript{41}), \textit{reaction speed} (FePsy Visual reaction times: dominant and non-dominant hand\textsuperscript{42}), \textit{motor speed} (FePsy Finger Tapping: dominant and non-dominant hand\textsuperscript{42}) and \textit{verbal fluency} (Categories animals and professions\textsuperscript{43},}
Letterfluency\textsuperscript{44}). Tests were selected for reliability, validity, sensitivity for effects of hormones and suitability for older age groups. The Dutch Adult Reading Test\textsuperscript{45} was used to estimate verbal intelligence.

**Statistical methods**

The Statistical Package for Social Sciences (SPSS) WINDOWS 17.0 was used for all analyses. Differences in sociodemographic characteristics between groups were analyzed by means of $\chi^2$ tests or univariate analysis of variance (ANOVA). Because age and IQ differed between patients and healthy controls, all subsequent analyses were adjusted for age and IQ.

The interview was used in two ways: the questions were considered separately, and in addition a scale (the ‘cognitive interview-scale’) was constructed out of the two general questions regarding memory and concentration complaints; each item was scored as 1 (complaint present) or 0 (no complaint present), the total score was the sum of the item scores (range 0-2, higher score means more complaints). Because no reliability information of this ‘cognitive interview-scale’ is known, we determined the Cronbach’s $\alpha$ (internal consistency) at T1 and T2 and Pearson’s correlations between T1 and T2 in the total study population. In addition, we determined similar reliability information for all other self-report measures. Data from self-report questionnaires were converted according to standard scoring rules.

Differences between groups at T1 on the self-report scales were evaluated by means of logistic regression (for the separate interview questions and the percentage of ‘possible depressive cases’) or ANOVA (for all other self-report measures). Differences between groups in change over time were analyzed by means of logistic regression (for the separate interview questions and the percentage of ‘possible depressive cases’) or ANCOVA (for all other self-report measures), in which the T2 scores were the dependent variables, and the T1 scores the covariates.

Overall cognitive test performance was expressed by the mean of the Z-scores of 18 cognitive tests. To determine this variable, raw cognitive test scores were converted to standardized Z-scores based on the mean and standard deviation of the healthy control group at, respectively, T1 and T2. Mean Z-scores of the healthy control group were zero.
both at T1 and T2. In this way, the T2 Z-scores accounted for test-retest effects, such as practice-effects, which are intrinsic to repeated cognitive testing.\textsuperscript{26}

For the total study population, associations between the two measures for self-reported cognitive functioning (cognitive interview-scale and CFQ), cognitive test performance, anxiety/depression, fatigue and menopausal complaints were assessed by means of Pearson’s correlations coefficients. Correlation coefficients were determined both at T1 and T2. For all analyses, a two-sided $P$-value less than 0.05 was required for significance.

\section*{Results}

\textit{Patients and healthy controls}

Three hundred and thirty-one TEAM patients were invited to participate in the neuropsychological study, of whom 206 (62\%) agreed. Ninety-two patients allocated to tamoxifen, 114 patients allocated to exemestane and 124 healthy controls underwent assessments at T1. Data at T2 were provided by 90\% of the participants (80 tamoxifen users, 99 exemestane users and 120 healthy controls). More patients than healthy controls were lost to follow-up (13.0\%, 12.4\% and 3.2\% of tamoxifen, exemestane versus controls respectively). The participants who were lost to follow-up were significantly older (72.3 versus 67.6 years; $P$\textless 0.01) and had lower IQ’s (93.9 versus 102.7; $P$=0.02) than participants completing both assessments. Sociodemographic information about the participants is shown in table 1.

\begin{table}[h]
\centering
\caption{Sociodemographics of the tamoxifen users, the exemestane users and the healthy controls}
\begin{tabular}{|l|ccc|}
\hline
 & Tamoxifen users (n=80) & Exemestane users (n=99) & Healthy controls (n=120) \\
\hline
Age; Mean (SD) & 68.7 (7.6) Range 51-84 & 68.3 (6.8) Range 50-82 & 66.2 (7.9) Range 49-86 \\
\hline
IQ; Mean (SD) & 100.7 (20.0) & 100.5 (18.6) & 105.8 (19.0) \\
\hline
T1-T2 interval in months; Mean (SD) & 12.4 (1.2) & 12.2 (1.4) & 12.3 (0.6) \\
\hline
Underwent Radiotherapy; % (n) & 58.8 (47) & 68.7 (68) & - \\
\hline
Ever-use of hormone replacement therapy \% (n) & 17.5 (14) & 20.2 (20) & 19.2 (23) \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}$P$-values for ANOVA (for age, IQ and T1-T2 interval) and $\chi^2$ test (for ‘self-reported adherence’, ‘T1-T2 interval’ and ‘underwent radiotherapy’).

\textsuperscript{b}Post-hoc tests: tamoxifen versus controls: $P$=.03; exemestane versus controls: $P$=.04; tamoxifen versus exemestane: $P$=.71.
Reliability of self-report instruments

The reliability of our composed ‘cognitive interview-scale’ (Cronbach’s α: 0.52; correlation between T1 and T2: 0.56) was below the limit that is usually regarded as satisfactory (0.7). This means that the scale does not measure the construct ‘self-reported cognitive functioning’ reliably. Therefore, we used the interview questions separately in addition to the composed scale. The reliability of the other self-report scales was satisfactory (Cronbach’s α 0.70 - 0.90, correlations between T1 and T2 0.58-0.76), see table 2.

Table 2. Reliability (Cronbach’s α and Pearson’s correlation between T1 and T2) of the self-report measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Internal consistency at T1 (Cronbach’s α)</th>
<th>Internal consistency at T2 (Cronbach’s α)</th>
<th>Correlation T1-T2 Pearson’s r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive interview-scale</td>
<td>0.52</td>
<td>0.52</td>
<td>0.56</td>
</tr>
<tr>
<td>CFQ</td>
<td>0.88</td>
<td>0.90</td>
<td>0.76</td>
</tr>
<tr>
<td>HSCL</td>
<td>0.89</td>
<td>0.89</td>
<td>0.58</td>
</tr>
<tr>
<td>EORTC QLQ-C30 fatigue scale</td>
<td>0.78</td>
<td>0.81</td>
<td>0.57</td>
</tr>
<tr>
<td>FACT-B ES</td>
<td>0.70</td>
<td>0.76</td>
<td>0.67</td>
</tr>
</tbody>
</table>

- Self-composed scale out of two questions regarding memory and concentration complaints.
- Cognitive failures questionnaire.
- Hopkins Symptom Check List.
- European Organization for Research and Treatment of Cancer Quality of Life questionnaire.
- Endocrine Subscale of the Functional Assessment of Cancer Therapy–Breast questionnaire.

Results of Patient Reported Outcomes (pro’s)

Self-reported cognitive functioning

Results of self-report measures for cognitive functioning are presented in table 3. At T1, (after surgery, but before the start of endocrine treatment), the three groups did not differ significantly with regard to the prevalence of self-reported cognitive complaints (B=-.12, P=0.48). At T2, adjusted for complaints at T1, the prevalence of concentration complaints differed significantly between the groups, due to more reported problems by tamoxifen users (B=.52, P=0.004). The three groups did not differ significantly with regard to the prevalence of memory complaints at T2 (B=.29, P=0.09). In addition, at T2, adjusted for T1 percentages, relatively more tamoxifen users than exemestane users and healthy controls, respectively, reported problems with ‘distractibility’ (B=.43, P=0.03), ‘sustained attention’ (B=.45, P=0.02) and ‘multitasking’ (B=.55, P=0.04).
Table 3. Self-reported cognitive functioning (Cognitive Interview and Cognitive Failures Questionnaire) at T1 and T2 in the tamoxifen, exemestane and healthy control group

<table>
<thead>
<tr>
<th></th>
<th>Baseline (T1)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>Exemestane</td>
<td>Healthy</td>
<td>P*</td>
<td>Tamoxifen</td>
<td>Exemestane</td>
<td>Healthy</td>
<td>P**</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>users (n=80)</td>
<td>users (n=99)</td>
<td>controls (n=120)</td>
<td></td>
<td>users (n=80)</td>
<td>users (n=99)</td>
<td>controls (n=120)</td>
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<tr>
<td>Memory complaints* % (n)</td>
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<tr>
<td>Forgetting appointments</td>
<td>45 (36)</td>
<td>38 (38)</td>
<td>38 (46)</td>
<td>0.23</td>
<td>54 (43)</td>
<td>47 (46)</td>
<td>41 (49)</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Losing one’s things</td>
<td>10 (8)</td>
<td>3 (3)</td>
<td>5 (6)</td>
<td>0.31</td>
<td>14 (11)</td>
<td>10 (10)</td>
<td>5 (6)</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Forgetting telephone</td>
<td>21 (17)</td>
<td>16 (16)</td>
<td>12 (14)</td>
<td>0.04</td>
<td>17 (13)</td>
<td>15 (15)</td>
<td>10 (12)</td>
<td>0.64</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>numbers</td>
<td>11 (9)</td>
<td>10 (10)</td>
<td>7 (8)</td>
<td>0.25</td>
<td>14 (11)</td>
<td>6 (6)</td>
<td>5 (6)</td>
<td>0.12</td>
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<tr>
<td>Concentration complaints* % (n)</td>
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</tr>
<tr>
<td>Distractibility</td>
<td>26 (21)</td>
<td>24 (24)</td>
<td>34 (41)</td>
<td>0.48</td>
<td>48 (38)</td>
<td>27 (27)</td>
<td>32 (38)</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Problems with sustained</td>
<td>20 (16)</td>
<td>16 (16)</td>
<td>24 (29)</td>
<td>0.68</td>
<td>31 (25)</td>
<td>18 (18)</td>
<td>23 (27)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>attention</td>
<td>16 (13)</td>
<td>8 (8)</td>
<td>14 (17)</td>
<td>0.66</td>
<td>33 (26)</td>
<td>16 (16)</td>
<td>18 (22)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Problems with multitasking</td>
<td>14 (11)</td>
<td>9 (9)</td>
<td>8 (10)</td>
<td>0.12</td>
<td>15 (12)</td>
<td>9 (9)</td>
<td>5 (6)</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Interview-scale</td>
<td>.71 (.83)</td>
<td>.63 (.71)</td>
<td>.73 (.80)</td>
<td>0.74</td>
<td>1.0 (.82)</td>
<td>.74 (.79)</td>
<td>.73 (.79)</td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFQ; mean (SD)</td>
<td>31 (11)</td>
<td>28 (11)</td>
<td>33 (8)</td>
<td>0.004</td>
<td>31 (12)</td>
<td>28 (11)</td>
<td>32 (9)</td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P-value of logistic regression; ** P-value of logistic regression adjusted for percentage at T1.

*aPercentage of participants expressing a complaint.

*bScale based on two interview questions (see Method section); range 0-2; higher score means more complaints.

*cCFQ; range 0-100, higher score means higher frequency of cognitive failures and lapses.
Table 4. Anxiety/depression (HSCL), fatigue (EORTC QLQ-C30) and menopausal complaints (FACT-B ES) at T1 and T2 in the tamoxifen, exemestane and healthy control group

<table>
<thead>
<tr>
<th></th>
<th>Baseline (T1)</th>
<th>Follow-up (T2)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tamoxifen users (n=80)</td>
<td>Exemestane users (n=99)</td>
<td>Healthy controls (n=120)</td>
<td>Tamoxifen users (n=80)</td>
</tr>
<tr>
<td><strong>Anxiety/Depression</strong>&lt;sup&gt;a&lt;/sup&gt;; mean (SD)</td>
<td>14 (11)</td>
<td>12 (11)</td>
<td>10 (9)</td>
<td>0.08</td>
</tr>
<tr>
<td><em>Possible depressive case</em>&lt;sup&gt;b&lt;/sup&gt;; % (n)</td>
<td>27 (22)</td>
<td>20 (20)</td>
<td>14 (17)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Fatigue</strong>&lt;sup&gt;c&lt;/sup&gt;; mean (SD)</td>
<td>34 (22)</td>
<td>32 (22)</td>
<td>18 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Menopausal complaints</strong>&lt;sup&gt;d&lt;/sup&gt;; mean (SD)</td>
<td>62 (7)</td>
<td>63 (6)</td>
<td>63 (6)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

<sup>a</sup>P-value of ANOVA; <sup>b</sup>P-value of ANCOVA, using the score at T1 as a covariate.

<sup>a</sup>HSCL; range 0-100, higher score means more serious symptoms.

<sup>b</sup>Possible depressive case defined as a mean HSCL item-score of ≥1.55.

<sup>c</sup>EORTC QLQ-C30 fatigue subscale; range 0-100, higher score means more serious symptoms.

<sup>d</sup>FACT-B Endocrine subscale; range 0-72, higher score means better functioning.
The results of the cognitive interview-scale confirmed the pattern found in the separate interview questions: no difference between groups in cognitive complaints at T1, but a significant difference between groups at T2, adjusted for T1 scores (F= 4.8, P=0.009). Tamoxifen users showed the largest mean increase in cognitive complaints.

The self-reported frequency of cognitive failures measured by the CFQ, was significantly different between the groups at T1, the healthy controls reporting the highest frequency of cognitive failures (F= 5.7, P=0.004). At T2, adjusted for T1 scores, no difference between the groups was found anymore (F= 0.6, P=0.54).

Anxiety/depression, fatigue and menopausal complaints

Table 4 shows the results for anxiety/depression, fatigue and menopausal complaints. At T1, patients reported more fatigue than healthy controls (F= 20.1, P=<0.001). With respect to anxiety/depression, the mean ratings at T1 did not differ significantly between groups, but the percentage of persons being classified as ‘possibly depressive cases’ was significantly different, being the highest in patients about to start with tamoxifen. For menopausal complaints no significant differences between the groups were observed at T1. At T2, adjusted for T1 ratings, both patient groups reported (a slight) increase in complaints at T2, while healthy controls reported (slightly) less complaints (F= 8.5, P=<0.001). For anxiety/depression and fatigue, no significant differences were observed between groups at T2, adjusting for T1 scores.

Associations between cognitive test performance, self-reported cognitive functioning, anxiety/depression, fatigue and menopausal complaints in the total study population

Both at T1 and T2, self-reported cognitive functioning as measured with the ‘cognitive interview-scale’ and the CFQ was weakly to moderately correlated with anxiety/depression ratings, with fatigue and with menopausal complaints. No statistically significant correlations were found between cognitive test performance and self-reported cognitive functioning, both at T1 and T2, using the cognitive interview-scale as well as the CFQ as self-report measure for cognitive functioning. Weak associations at both assessment points were found between cognitive test performance and ratings of anxiety/depression and of fatigue. No significant associations between cognitive test performance and menopausal complaints were found, see table 5.
Table 5. Pearson’s correlations (adjusted for age/IQ) between self-reported cognitive functioning, anxiety/depression, fatigue, menopausal complaints and cognitive test performance

<table>
<thead>
<tr>
<th></th>
<th>Baseline (T1)</th>
<th>Follow-up (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cognitive complaints(^a)</td>
<td>Fatigue(^b)</td>
</tr>
<tr>
<td>Cognitive complaints(^a)</td>
<td>0.29(^*)</td>
<td>0.15(^*)</td>
</tr>
<tr>
<td>Cognitive failures(^b)</td>
<td>0.11</td>
<td>0.22(^*)</td>
</tr>
<tr>
<td>Fatigue(^c)</td>
<td>0.51(^*)</td>
<td>-0.35**</td>
</tr>
<tr>
<td>Anxiety/Depression(^d)</td>
<td>-0.45**</td>
<td>-0.13*</td>
</tr>
<tr>
<td>Menopausal complaints(^e)</td>
<td>0.09</td>
<td>-0.06</td>
</tr>
</tbody>
</table>

*P-value of correlation <0.05; **P-value of correlation <0.01.
\(^a\)Cognitive interview-scale based on two interview questions (see Method section); range 0-2; higher score means more complaints.
\(^b\)CFQ; higher score means higher frequency of cognitive failures.
\(^c\)EORTC QLQ-C30 fatigue subscale; higher score means more serious symptoms.
\(^d\)HSCL; higher score means more serious symptoms.
\(^e\)FACT-B Endocrine subscale; higher score means better functioning.
\(^f\)Mean Z-score of 18 cognitive tests.
Discussion

To our knowledge, this is the first study investigating self-reported cognitive functioning in postmenopausal breast cancer patients receiving adjuvant endocrine treatment that included (1) baseline assessments before the start of endocrine treatment and (2) comparisons with healthy controls.

The interview results regarding cognitive complaints show that at baseline (T1) the proportion of postmenopausal breast cancer patients reporting cognitive complaints is not higher than in healthy controls. After one year of endocrine treatment (T2), an increased percentage of patients complaining about their concentration was only observed in the tamoxifen group. With respect to memory, the percentage of participants reporting complaints increased slightly in all three groups, without a significant difference between the three groups with respect to the degree of increase.

The results on the cognitive failures questionnaire (CFQ) showed no change over time in any of the three groups. As this pattern differs from our observations from the interview it indicates that distinct aspects of self-reported cognitive functioning (complaints versus frequency of cognitive failures) might not give uniform information regarding self-reported cognitive functioning. The strength of the correlations between the two measures, which was only moderate (0.29-0.32), confirms the different nature of the two self-report measures. A possible explanation for the lack of change over time observed in the CFQ-scores may be that the CFQ is thought to assess ‘proneness to subjective cognitive failures’ which seems to be a stable characteristic, expressed across a variety of situations. A lack of change over time in CFQ-scores has also been found in earlier studies performed in breast cancer patients receiving the aromatase inhibitor anastrozole and in healthy older adults, respectively. With respect to the interview regarding memory and concentration complaints, up till now little is known about the stability of the measured characteristic(s) and the reliability/validity of observed changes in percentages of persons expressing the complaints.

Our results suggest that the use of tamoxifen, but not of exemestane, might be associated with an increase in self-reported concentration complaints, which is the first report hereon. Up till now, few studies evaluated self-reported cognitive complaints in relation to
specific endocrine treatments. In one retrospective study, more women having used tamoxifen for 5 years or longer reported to have consulted a physician for memory problems in comparison with non-tamoxifen users. In women at increased risk for breast cancer who used either anastrozole or placebo, memory changes were reported by 13% of the women without differences between the anastrozole and the placebo group. As this analysis is the first to provide information regarding self-reported cognitive functioning by exemestane users, comparison data are not available. Considering the results of the two former studies and the current analysis together, the data suggest that tamoxifen is more strongly linked to self-reported cognitive complaints than AIs. This finding is interesting especially in the light of our findings with respect to cognitive test performance, which indicate that tamoxifen also has a more negative impact on certain cognitive functions than the AI exemestane. In our opinion, it shows that tamoxifen has a larger impact on both cognitive test performance and on self-reported cognitive functioning than AIs. The precise impact hereof, however, is not yet clear as we did not find an association between cognitive test performance and self-reported cognitive functioning.

The fact that we did not find an association between self-reported cognitive functioning and cognitive test performance is in concordance with previous findings. In our data, there was no difference between correlations obtained with the CFQ (with satisfactory reliability) or the self-composed ‘cognitive interview-scale’ (with non-satisfactory reliability). This suggests that the reliability of self-report scales cannot account for the lack of associations between self-reported cognitive functioning and cognitive test performance.

In the literature, the construction of cognitive assessments having better ecological validity and the construction of self-report measures being a more valid representation of cognitive functioning have been suggested to enhance the concordance between cognitive test performance and self-reported cognitive functioning. Notwithstanding the importance of initiatives to improve the reliability/validity of cognitive tests and self-report measures, it is questionable to what extent this actually would lead to satisfactory correlations, given the distinctive predictive factors for self-reported cognitive functioning and cognitive test performance, respectively. As a consequence, questions regarding cognitive complaints and instruments to measure self-reported cognitive functions are currently not useful as substitutes for cognitive test performance. Nevertheless, several
authors\textsuperscript{3,49} stressed that the inclusion of self-reports of cognitive functioning in studies on the cognitive effects of systemic cancer treatments is important in order to understand the patients’ experiences and concerns associated with the disease and various treatments. Further studies on the impact of endocrine therapies for breast cancer patients on both self-reports of cognitive functioning and cognitive test performance are greatly warranted, the more because this type of therapy is given for a prolonged period of time (preferentially for at least 5 years).

Also in accordance with previous studies, we observed weak associations between cognitive test performance and anxiety/depression and fatigue, respectively. Although the strengths of these associations were weak, anxiety/depression and fatigue might be variables that have to be taken into account when investigating the impact of cancer and cancer therapies on cognitive functioning. Finally, the associations we observed between self-reported cognitive functioning and anxiety/depression and fatigue are in accordance with data from previous research.\textsuperscript{1,48}

The question of the clinical relevance of cognitive complaints remains unanswered yet. In our study population, cognitive complaints were expressed by a substantial part of the breast cancer patients both before and during endocrine treatment, but also by a substantial part of the healthy controls. In order to increase the understanding of the clinical relevance of cognitive complaints in breast cancer patients, future studies should take into account the knowledge that is derived from studies on self-reported cognitive functioning in normal aging groups. In this respect, it has been shown that an individual’s belief about memory ability in various situations, as well as knowledge and beliefs about the effects of aging on cognitive functioning are relatively stable over time\textsuperscript{22} Furthermore, it has been reported that knowledge about relationships between systemic treatment for cancer and cognitive complaints, if present in a particular patient might influence self-reports of cognitive functioning.\textsuperscript{4}

For the moment, clinicians have to face the problem to distinguish between cognitive complaints that are related to cognitive impairments secondary to brain dysfunctions versus those related to, for example, mood, fatigue and/or adjustment difficulties. The evidence is growing that systemic cancer therapies, including endocrine treatments for breast cancer such as tamoxifen, might affect cognitive test performance.\textsuperscript{26,50} It is also
known that cognitive complaints might be associated with feelings of anxiety, depression and/or fatigue. So, patients presenting with cognitive complaints might benefit from information about the associations between cognitive complaints and being diagnosed with cancer, therapies for cancer, and anxiety/depression and fatigue, respectively. In case of lasting cognitive complaints, we would advocate proceeding to additional assessment by means of neuropsychological examinations, also including issues as mood and fatigue, in order to determine the most appropriate counseling or treatment options for that particular patient.

Acknowledgements

We are indebted to all patients, healthy controls as well as physicians and research nurses of 38 Dutch hospitals that participated in this cognitive study. We are also grateful to the Datacenter Heelkunde of the Leiden University Medical Center for organizational support and to M. Weevers, S. Leering and A. van Nuland for helping collecting the data. This original work was supported by an independent research grant from Pfizer, grant number 56850.
Chapter 7

Reference List


Self-reported cognitive functioning before and during endocrine treatment


(31) Huyser Y. *De symptomatologie van depressieve stoornissen en angststoornissen.* Amsterdam: Benecke Consultants; 2004.


Chapter 8

Summary of results and general discussion
Chapter 8

Introduction

In this chapter, the aims and main conclusions of the studies are presented. In addition, several methodological issues that have arisen from the studies will be discussed. The chapter concludes with issues regarding the interpretation of the findings, implications for clinical practice and recommendations for future research.

Aims of the thesis

The primary aim of this thesis was to investigate the impact of two types of adjuvant endocrine treatment, tamoxifen and exemestane, on cognitive functioning in postmenopausal breast cancer patients. Endocrine treatment is an important option for patients with hormone-sensitive breast cancer. For decades, tamoxifen (a selective estrogen receptor modulator [SERM]) was the standard adjuvant endocrine treatment for post-menopausal women. The use of 5 years of tamoxifen is associated with a 41% relative risk reduction of recurrence of breast cancer and a 34% relative risk reduction of death in patients with hormone-sensitive breast cancer. The advantage of 5 years of tamoxifen over no adjuvant treatment persists even after a follow-up period of 15 years. More recently, several clinical trials showed that including an aromatase inhibitor (AI) in adjuvant endocrine therapy, for example anastrozole, letrozole or exemestane, further improves survival. Ongoing trials are exploring the optimal duration of adjuvant endocrine therapy, as well as the most effective choice and sequence of agents. Although generally well tolerated, endocrine treatments have side effects which are of clinical concern and are predictive of non-adherence to the treatment regimen. Many side effects of endocrine therapy, such as hot flashes and mood disturbances, are related to estrogen deprivation and are common to tamoxifen and AIs. In addition, tamoxifen has estrogenic effects that are beneficial in some tissues: tamoxifen lowers serum cholesterol levels and protects against bone loss and cardiovascular disease, but is also associated with a higher risk of endometrial cancer and thromboembolic disease. AIs are associated with a lower incidence of gynecological symptoms and hot flashes than tamoxifen. However, AIs are associated with musculoskeletal side effects, such as arthralgia, myalgia and bone loss.
The rationale behind this study, specifically focusing on potential effects of endocrine treatments on cognitive functioning, can be found in the increasing evidence that estrogens are important for cognitive functioning. This raised questions about possible detrimental effects of endocrine treatments for breast cancer, which aim at estrogen deprivation, on cognitive functioning. Evaluation of possible effects of endocrine treatments is relevant, because intact cognitive functioning is important for wellbeing and independent living of patients. The randomized Tamoxifen and Exemestane Multinational trial (TEAM trial) provided the opportunity to study the effects of two different types of endocrine treatment, the SERM tamoxifen and the AI exemestane on cognitive functioning in a prospective way.

The prospective design included baseline cognitive assessments. This enabled us to evaluate cognitive functioning after surgery, but before the start of adjuvant endocrine treatment. This is important because several prospective cognitive studies in breast cancer patients reported cognitive impairment that was already present before the start of adjuvant systemic treatment. Up till now, the origin and extent of this pre-treatment cognitive impairment are unclear. Possible explanations postulated in the literature include the impact of psychological distress on cognitive functioning, or negative effects of anesthesia and surgery undergone in the weeks before the baseline cognitive assessment. The extent to which pre-treatment cognitive impairment is observed might also be dependent on the methodology used to describe cognitive performance. A secondary aim of this thesis was to increase the understanding of cognitive functioning prior to adjuvant systemic (endocrine) treatment. We evaluated the pre-treatment cognitive functioning from two different points of view: first, we targeted methodological aspects regarding the use of pre-defined criteria for cognitive impairment and the choice of a reference group (published normative data versus a study-specific healthy control group). We classified participants as ‘cognitively intact’ or ‘cognitively impaired’ according to different criteria for cognitive impairment and different reference groups in order to highlight the contrasting results of these different methods. Secondly, we compared, at a group level, cognitive functioning of postmenopausal breast cancer patients before the start of endocrine treatment with that of healthy controls and evaluated to what extent medical and psychological factors explained the differences in cognitive functioning between breast cancer patients and healthy controls.
A growing number of patients receive endocrine treatment after completion of chemotherapy. The TEAM trial also provided the opportunity to evaluate cognitive functioning in breast cancer patients who were exposed to both chemotherapy and endocrine treatment. We did this in an additional, cross-sectional study in which we compared cognitive functioning of patients who received tamoxifen with patients who received exemestane after treatment with doxorubicin/cyclophosphamide (AC) chemotherapy. Furthermore, we pooled the tamoxifen and the exemestane groups into one patient group and compared cognitive functioning in this combined patient group with that of healthy controls.

In order to obtain a more complete picture of the possible influence of endocrine treatments on cognitive functioning, we included ‘patient-reported outcomes’ (PROs) on cognitive functioning in addition to cognitive test performance. PROs are measurements of aspects of a patient’s health status that come directly from the patient without interpretation of the patient’s response by a clinician or anyone else. They are particularly important in clinical trials in which two treatments with similar efficacy may have different safety profiles that have an impact on patients’ symptoms, functioning, or health-related quality of life (HRQoL). PROs may complement and extend information provided by clinical end points on the efficacy and side-effects of treatment. In this thesis, PROs were used to evaluate self-reported cognitive functioning in tamoxifen users, exemestane users and healthy control women, and to evaluate associations between self-reported cognitive functioning and cognitive test performance. Because it is known from the literature that symptoms of anxiety/depression, fatigue and menopausal complaints might play a role in both self-reported cognitive functioning and cognitive test performance, the associations of self-reported cognitive functioning with these variables also were evaluated.

Synopsis of the key findings

Chapter 2 provides a summary of the literature about the possible effects of estrogens and endocrine therapy for breast cancer on cognitive functioning in aging women. The effects of estrogens on cognitive functioning in aging women have been evaluated in numerous studies. The results of these studies indicate that the natural menopausal transition is not, or at the most, weakly associated with cognitive decline. On the contrary, surgical menopause has an effect on verbal memory functioning coincident with changes in plasma estrogen levels, indicating that abrupt lowering of estrogen levels is associated
with cognitive decline. Studies that evaluated the effects of hormone replacement therapy (HRT) on cognitive functioning also provide evidence for cognitive effects of estrogen. Summarized, these studies provide evidence for beneficial effects when HRT is administered in the years close to the menopausal transition, but for no, or even detrimental effects when administered many years after menopause.\textsuperscript{15,16} Although the nature of the possible effects of estrogens on cognitive functioning is becoming more apparent due to extensive study in recent years, the potential effects of endocrine therapies for postmenopausal breast cancer patients, aiming at estrogen deprivation, on cognitive functioning have only been evaluated to a limited extent. Studies evaluating tamoxifen suggest small detrimental effects on cognitive functioning\textsuperscript{17-19}, while studies on anastrozole (the only AI for which cognitive data are available) report conflicting results with regard to its effect on cognition.\textsuperscript{18-21}

In \textbf{Chapters 3 and 4}, two studies with regard to cognitive functioning before the start of endocrine treatment are described. One of the methods to investigate cognitive functioning is to classify the participants as ‘cognitively impaired’ or ‘cognitively intact’ according to a pre-defined criterion and compare the proportion of ‘cognitively impaired’ patients with the proportion found in a reference group. In the literature regarding cancer and cognition many different criteria, as well as different types of reference groups are used, resulting in substantial differences in the observed prevalence of cognitive impairment leaving questions on actual percentages of patients affected unanswered.\textsuperscript{22} In \textbf{Chapter 3}, the impact of four different criteria for cognitive impairment (failure on ≥4, ≥3, ≥2 and ≥1 tests respectively) and two types of reference groups (our own study-specific healthy reference group versus published normative data) on the prevalence of cognitive impairment was examined. The patient group consisted of 205 postmenopausal breast cancer patients (mean age 68.9 years) who were about to start with endocrine treatment. The study-specific healthy reference group consisted of 124 postmenopausal friends and relatives of the patients (mean age 66.5 years). The prevalence of cognitive impairment varied greatly with the strictness of the criterion, as expected, but also was dependent on the reference group used. Cognitive impairment, relative to published norms, ranged from 1% for the most strict to 36.6% for the least strict criterion. Cognitive impairment relative to study-specific healthy controls, ranged from 13.7 to 45.4% for the same criteria. This study highlights the contrasting proportions of patients classified as ‘cognitively impaired’ by using different criteria for cognitive impairment and different reference groups.
Furthermore, it stresses the need for consensus on the measures and statistical methods to study cognitive impairment both before and during/after adjuvant systemic therapy. The second study (Chapter 4) aimed to identify medical and psychological predictors for cognitive performance of breast cancer patients before the start of adjuvant systemic treatment, and to compare cognitive test performance between breast cancer patients and healthy controls adjusting for medical and psychological variables. In this chapter, we analyzed the data of the same group of patients (n=205, mean age 68.9 years) and healthy controls (n=124, mean age 66.5 years) on a group-level. We found that ‘treatment for diabetes mellitus’ and/or ‘hypertension’, ‘less hours spent on cognitively stimulating activities’, ‘fewer days since surgery’ and ‘more reproductive years’ were associated with lower cognitive performance in the breast cancer patients, independent of age and IQ. These medical and psychological variables explained a modest 1-6% of the variance in addition to the 10-40% of the variance explained by age and IQ. Cognitive differences between breast cancer patients and healthy controls could partially be explained by the evaluated variables, but a small-to-medium unexplained difference remained. The results stress the need for adjustment for pre-treatment cognitive differences between study groups, and also indicate that further research into the cause of pre-treatment cognitive dysfunction is warranted.

Chapter 5 describes the core study of this thesis, a prospective neuropsychological study involving 38 hospitals in the Netherlands investigating the effects of tamoxifen and exemestane on cognitive functioning of postmenopausal breast cancer patients who had not received chemotherapy. Patients were TEAM trial participants who were randomized between tamoxifen (n=80, mean age = 68.7 years) or exemestane (n=99, mean age 68.3 years) after surgery with a curative intent. All patients underwent neuropsychological examinations before the start of tamoxifen or exemestane treatment (T1), and after one year of continuous treatment (T2). In order to take practice effects, which are inherent to neuropsychological testing, into account, a healthy control group consisting of friends and relatives of the patients underwent the same tests twice at an interval of 1 year. Eight cognitive domains were created out of 18 test indices. After one year of treatment (T2) and after adjustment for T1 performance, exemestane users did not perform statistically significantly worse than healthy controls in any cognitive domain. In contrast, tamoxifen users performed statistically significant worse than healthy controls on verbal memory and executive functioning and statistically significantly worse than exemestane users on
information processing speed. With respect to visual memory, working memory, verbal fluency, reaction speed and motor speed, no significant differences between the three groups were found. All effect-sizes were in the small-to-medium range.

In clinical practice, many patients who receive endocrine treatment also received treatment with chemotherapy in the past. From previous research at the Netherlands Cancer Institute and in other research groups it is known that chemotherapy might be associated with cognitive impairment in a subgroup of patients\(^{24-26}\), depending on the specific regimen applied. To explore the impact of chemotherapy, followed by tamoxifen or exemestane on cognitive functioning, we performed a cross-sectional study described in Chapter 6. In this study, TEAM trial patients who received standard-dose adjuvant chemotherapy before the start of endocrine treatment participated. The patients were randomized between tamoxifen (n=30, mean age 57.9 years) or exemestane (n=50, mean age 58.5 years) after doxorubicin/cyclophosphamide (AC) chemotherapy and completed chemotherapy on average 2 years before the neuropsychological assessment. In addition, a reference group consisting of healthy women of approximately the same age was included (n=48, mean age 60.2 years). These healthy women were selected from the prospective study (see Chapter 5) on the base of the age and IQ distribution of the patients. On 18 measures of cognitive functioning, patients receiving tamoxifen were compared with patients receiving exemestane, and the combined patient group was compared with the healthy reference group. Cognitive testing revealed no statistically significant differences between tamoxifen and exemestane users, but suggested that tamoxifen use is possibly related to worse verbal functioning, while exemestane use is possibly related to slower manual motor speed. Both patient groups performed significantly worse than healthy controls on tests of verbal fluency and information processing speed. This study showed that sequential treatment of AC-chemotherapy and hormonal therapy in postmenopausal breast cancer is associated with lower test scores for certain cognitive functions, and provides indications of possibly distinctive associations for different types of hormonal treatment. No correlations between cognitive performance and anxiety/depression ratings were observed. Memory complaints (defined as having a frequency of at least ‘regularly’) were reported by 28% of AC/tamoxifen users, 24% of AC/exemestane users and 6% of healthy controls.
The study described in Chapter 7 focuses on self-reported cognitive functioning of breast cancer patients who use tamoxifen or exemestane. We aimed (1) to evaluate self-reports on cognitive functioning of postmenopausal breast cancer patients undergoing adjuvant endocrine treatment with tamoxifen or exemestane compared to healthy controls, and (2) to explore associations between self-reported cognitive functioning, cognitive test performance, anxiety/depression, fatigue and menopausal complaints. The participants were the same as in the core-study of this thesis (Chapter 5): TEAM trial participants who were randomized between tamoxifen (n=80, mean age = 68.7 years) or exemestane (n=99, mean age 68.3 years) after surgery with a curative intent. They provided data on self-reported cognitive functioning (both interview data regarding cognitive complaints as questionnaire data regarding the frequency of everyday cognitive failures and lapses). Furthermore, they provided questionnaire data on anxiety/depression, fatigue and menopausal complaints, and underwent cognitive assessments before (T1) and after one year (T2) of adjuvant endocrine treatment. Identical information was obtained from healthy postmenopausal volunteers (n=120). At T1, the three groups did not differ significantly with regard to the prevalence of self-reported cognitive complaints. At T2, adjusted for complaints at T1, the prevalence of concentration, but not of memory complaints differed significantly between the groups, due to an increase among tamoxifen users. The frequency of reported cognitive failures was not different between groups at T2, adjusted for T1 scores. Cognitive test performance was not associated with self-reported cognitive functioning. Self-reported cognitive functioning showed moderate associations with anxiety/depression, fatigue and menopausal complaints. Cognitive test performance was weakly associated with anxiety/depression and fatigue. Our results indicate that self-reports on cognitive functioning can not be regarded as substitutes for cognitive test performance, but might be more indicative for the level of, among others, anxiety/depression and fatigue.
Methodological considerations

This paragraph discusses the major methodological strengths and weaknesses of the study in more general terms.

Participation rate

Recruiting participants for clinical and neuropsychological studies is often a difficult task. Low participation rates undermine statistical power, increase the probability of bias and limit the ability to generalize the results. Loss of eligible patients may occur in several ways: patients may be recruited selectively, and patients may decline participation.

As in many studies in the social sciences, potential loss of eligible patients was a threat in our study. Selective recruitment of patients might have occurred on two occasions: (1) the physicians might have asked patients selectively for participation in the TEAM trial and (2) the physician might have asked patients selectively to participate in the neuropsychological side study. On three occasions, patients could actively decline participation: they could decline participation in the TEAM trial itself (3), they could decline participation in the neuropsychological side study (4) and they could decline participation in the follow-up measurement (5).

With respect to selective recruitment (occasion 1) and active decline of patients for the TEAM trial (occasion 3) no data are available. In the case of occasion 2, 53 of the 393 eligible patients were missed due to starting problems or other organizational problems in the hospitals, or because the oncologist found them not suitable for the study (n=9) due to, for example advanced age (n=2) or, interestingly, cognitive dysfunction (n=3). Of the 331 patients who were asked to participate in the neuropsychological side study, 125 (38%) actively declined participation (occasion 4). A factor that might have played a role in the less than optimal participation rate is the way in which participation was requested. Our intent was for oncologists and research nurses to only briefly introduce the study to eligible patients, hand over an information leaflet and ask for the patient’s permission to be called by the researchers. In a subsequent telephone call we would provide more information about the study and patients could then decide whether or not to participate. In practice this way of recruiting patients did not work well. Despite our repeated instructions to the hospital and the datacenter, we only received contact information for patients who already had decided to participate. We did not have the opportunity to get
in touch with the other patients to provide additional information or answering questions, which potentially would have influenced their decision to participate. Finally, loss to follow-up (declining on occasion 5) was limited to 13% of the patients.

The participation rate of the cross-sectional study among breast cancer patients who received chemotherapy before their participation in the TEAM trial was 85%, higher than for the prospective study. One of the reasons for this higher participation rate could be the fact that we contacted the patients directly, circumventing possible loss of participants on occasion 2. Other reasons might be the younger age of the patients, the fact that less effort was required (one assessment instead of two) and the fact that they were asked in a less overwhelming situation (2-4 years after the diagnosis) than the patients who were eligible for the prospective study.

The participation rate of the healthy control women is unknown because they were recruited by the participating patients, and we had no information about the number of friends and relatives that declined participation. Loss to follow-up was limited to 3% of all participating healthy control women.

To what extent were participation rates and loss to follow-up a threat for the potential to generalize of our study results? Especially when attrition of patients is not random, the probability of non-intended selection of participants is high. From the available data, we can conclude that a considerable number of patients (n=53) was missed due to organizational problems in the hospital, such as problems with starting up the inclusion procedure, high work-load or loss of interest on the part of physicians. As this loss of potential patients might be predominantly random, the amount of bias introduced is probably limited. The nine patients who were missed because their physician considered them unsuitable for the study might have introduced some bias, as it concerned mostly old and cognitively frail patients. The participation rate of TEAM trial participants who were asked to participate in the neuropsychological side study (respectively 62% and 85%) is comparable to similar studies, but participating patients might represent a non-intended selection of patients, for example patients who were in relatively good health, interested in the topic or are at ease with cognitive testing. We tested for possible age differences and concluded that there were no age-differences between the participants and non-participants. With respect to the healthy control group, some degree of selection bias
might be introduced as the patients, in general, tended to invite a relatively young and healthy friend or relative (mean age of patients 68.9, of healthy controls 66.5 years of age).

Loss to follow-up in our prospective study was limited to 13% of the patients and 3% of the healthy controls, which is an important strength of our study. Nevertheless, loss to follow-up seemed not to be completely random, as participants who were lost to follow-up were significantly older (72.3 versus 67.6 yrs; \( P \leq 0.01 \)) and had a lower IQ (93.9 versus 102.7; \( P=0.02 \)) than participants who completed both assessments.

In summary, the participation rate in our studies was suboptimal and non-participation was not completely random, as participants might be healthier and more interested and more at ease with cognitive testing than non-participants. Probably, this induced some degree of bias, which limits the ability to generalize of the results. For future studies, it is recommended to increase the possibilities to control the inclusion of patients and healthy controls, for example by the ability to contact all eligible participants directly, and monitoring the inclusion process of the healthy controls.

**Sample size and statistical power**

Given the knowledge derived from previous studies on the effects of estrogens and anti-estrogenic treatment on cognitive functioning, large cognitive effects of endocrine treatment are not to be expected. Therefore, studies need relatively large sample sizes in order to have satisfactory statistical power. The sample size of our prospective study (80 tamoxifen users, 99 exemestane users and 120 healthy controls) was large compared to other neuropsychological studies with cancer patients. We had a statistical power of at least 76% to detect differences in test scores of 0.4 standard deviations between the groups. Our sample sizes in the cross-sectional study among TEAM trial participants who received chemotherapy before the start of endocrine treatment were smaller (30 tamoxifen users, 50 exemestane users and 48 healthy controls). The lack of statistically significant differences between the tamoxifen- and the exemestane group on cognitive functioning might thus be a result of the insufficient statistical power to detect differences.
Randomized study with additional healthy control group

The randomized character of the TEAM trial, in which breast cancer patients were randomly allocated to tamoxifen or exemestane, resulted in two patient groups in which important confounding factors such as age and age-related comorbidity, sociodemographic background and prognosis were well balanced. The healthy control group, included in the study in order to take into account test-retest effects, was not composed in a randomized way. We chose for a control group consisting of healthy female friends and relatives of the patients in order to minimize differences in social and cultural background between patients and controls. A drawback of this non-randomized control group is the possible introduction of known and unknown sociodemographic, medical and psychological differences between the patients and the healthy controls, which might be of influence on cognitive functioning. Although we collected information about many potentially important variables and used statistical procedures in order to take into account the cognitive differences that were present before the start of endocrine treatment, the question remains whether such a statistical adjustment was sufficient to manage the pre-existing cognitive differences completely.

Prospective study

Our main study (Chapter 5) had a prospective design. An important strength of a prospective study is the possibility to study causal relationships and to study changes over time. Nevertheless, the determination of a causal relationship between different treatments and cognitive functioning might be problematic because other variables that could influence cognitive functioning might change simultaneously in the year between the first and second assessment. In this study such variables could be related to the diagnosis of cancer and other treatments, changes in health, changes in (prescription) medications, important life events etc. We were able to adjust for several variables that appeared to have changed over time in the patients and healthy controls, i.e. anxiety/depression, fatigue and menopausal complaints. These adjustments did not change the results, suggesting that these variables did not drive the relationship between the endocrine treatment and cognitive functioning.
Selection of cognitive domains and cognitive tests

At the time this study was started, the topic of cognitive effects of endocrine treatment for breast cancer had hardly been studied. In the few published neuropsychological studies at that time, only very small test batteries (2 or 3 tests) were used. These tests represented a diversity of cognitive domains, but a rationale for the cognitive domains of choice was not given. For the selection of the cognitive tests used for this thesis, we referred to the literature about effects of estrogens on cognitive functioning. The literature provided some evidence that the influence of estrogen on cognitive functioning is restricted to several specific cognitive domains, such as verbal memory, information processing speed and aspects of executive functioning. An appropriate selection of test should include tests covering these domains. However, consensus about the cognitive domains that are exclusively vulnerable to the effects of estrogen or endocrine treatment for breast cancer was lacking. In order to make sure inclusion of all relevant cognitive domains, we composed a battery of tests that covered a wide range of cognitive domains.

Selection of Patient-reported outcomes (PROs)

Self-reported cognitive functioning

In addition to the neuropsychological tests, we used several measures for self-reported cognitive functioning. Because no consensus exists in the literature about the best way to assess self-reported cognitive functioning, we used two distinctive measures. First, we interviewed all participants about the presence of complaints regarding memory, concentration, thinking and language. If a complaint in a particular domain was present, we asked the participant to give examples, and to provide indications about the frequency of complaints and the extent the complaint hindered them in daily life. This semi-structured interview was used earlier in cancer populations to compare the prevalence of cognitive complaints between groups of cancer patients who underwent different treatments. Secondly, we used the Broadbent cognitive failure questionnaire, a 25-item questionnaire measuring (on a 5-point scale) the frequency of everyday cognitive failures or lapses. These concern failures on memory, attention, action and perception. This measure has been evaluated as having good internal consistency, retest reliability and face validity in a cohort of older adults.
Anxiety/depression, fatigue and menopausal symptoms

We selected several self-report questionnaires to gather important quality of life information. Because these variables may act as covariates in the analyses of self-reported cognitive functioning and cognitive test performance, such information was important to obtain. For the measurement of symptoms of anxiety/depression the 25-item Hopkins Symptom Checklist (HSCL-25) was used, a sensitive case finder of clinically important depressive states in elderly populations.\(^3^0\) For fatigue, the 3-item fatigue subscale of the EORTC QLQ-C30 was used. This subscale has been shown to be a reliable and valid measure of fatigue in clinical research settings.\(^3^1\) Common side effects of endocrine treatment include menopausal symptoms. To investigate possible influences of menopausal symptoms on both self-reported cognitive functioning and cognitive test performance, we included the FACT-B Endocrine symptoms questionnaire, a reliable and valid questionnaire that is sensitive to clinically significant change.\(^3^2\)

Choice for statistical method to evaluate prospective data

The prospective study (Chapter 5) included three groups (tamoxifen users, exemestane users and healthy controls) and two measurements (patients had cognitive assessments before the start of treatment and after one year of treatment, healthy controls were assessed twice at an interval of 1 year). The patients were randomly allocated to either tamoxifen or exemestane, but the healthy control group was not selected on the basis of randomization. In a design with two or more groups and two repeated measurements, different statistical approaches are possible. The neuropsychological literature did not provide clear guidance on a choice between the approaches. The two most common statistical approaches are: (1) analysis of variance (ANOVA) of the change from the baseline, defined as follow-up score minus baseline score, and (2) analysis of covariance (ANCOVA) with the follow-up score as the outcome and the baseline score as a covariate.\(^3^3,3^4\) An advantage of the ANCOVA method over the ANOVA of change scores is that the ANCOVA method estimates the slope \(\beta\), whereas the ANOVA of change scores assumes that the slope \(\beta = 1\). In most situations, this ANCOVA method is regarded as more reliable and powerful than the ANOVA of change scores.\(^3^3,3^5\) For both methods, however, homogeneity of regression slopes between the groups is assumed. We tested this assumption, concluded that it was not violated and chose for the ANCOVA method.
As stated before, a complicating factor was the mixed design with respect to the randomization. As a consequence, some comparisons were between randomized groups and other comparisons were between non-randomized groups. As baseline differences between the groups might result in differential bias in both methods, we analyzed our data with both methods in order to evaluate potential differences in the results. The ANOVA of change scores did not reveal different results from the ANCOVA, so we could maintain the ANCOVA approach in the knowledge that the results of both approaches were comparable.

**Interpretation of findings**

In the previous sections, the findings of the studies in this thesis are described, as well as some methodological considerations. We noticed that the non-randomized character of the healthy control group and the suboptimal statistical power, particularly in the cross-sectional study, were limitations in these studies. Nevertheless, given the clear advantages of these studies such as the comprehensive neuropsychological test battery, the choice of cognitive domains, the large number of self-report measures, the fact that the patients were randomized between tamoxifen and exemestane treatment, the results of all studies together give a good approximation to be discussed in terms of their meaning and their potential origin.

**Differences between effects of tamoxifen and exemestane on cognitive functioning**

At the time that we started this study, the evidence for beneficial effects of estrogen on the brain and on certain cognitive functions was increasing. AIs, such as exemestane, almost completely inhibit the action of the enzyme aromatase, which is required for the peripheral conversion of androgens into estrogens. Consequently, AIs lower the level of circulating estrogen by almost 100%. Based on the putative beneficial effects of estrogens on cognitive functioning, together with the fact that exemestane lowers estrogen levels almost to zero, we hypothesized a detrimental effect of exemestane on cognitive functioning, which might be limited to certain cognitive domains.

Tamoxifen’s mechanism of action differs from that of the AIs. Tamoxifen binds to estrogen receptors, but whether its action is estrogenic or anti-estrogenic depends on the tissue. For example, on breast tissue, tamoxifen exerts anti-estrogenic effects, while on bone or
endometrial tissue, tamoxifen has estrogenic effects. It is not known whether tamoxifen has specific estrogenic or anti-estrogenic effects on brain tissue, hampering the possibility to formulate hypotheses about the effects of tamoxifen on cognitive functioning. The limited literature about cognitive effects of tamoxifen indicated small negative effects\textsuperscript{17-20}. Based on the existing literature, we hypothesized detrimental effects on cognitive functioning for tamoxifen, and again, potentially limited to certain cognitive domains, for example verbal memory.

We could not formulate hypotheses about differences in cognitive effects between tamoxifen and exemestane, although we could not rule out cognitive differences because of the different mechanisms of action of both agents. Possible differences in cognitive effects between the two agents were investigated in an exploratory/hypothesis-generating way.

With respect to exemestane, our hypothesized negative cognitive effects were not confirmed by our findings. This indicates that in postmenopausal breast cancer patients, lowering of estrogen levels does not result in measurable cognitive effects. Another explanation might be found in the mild androgenic properties of exemestane.\textsuperscript{38} Because androgens might be beneficial for performance in several cognitive domains\textsuperscript{39}, detrimental effects on cognitive function of estrogen deprivation might be limited, or even prevented by the androgenic properties of exemestane. Future head-to-head comparison of the cognitive effects of exemestane and other AIs that have no androgenic properties (for example anastrozole and letrozole) will be important in order to determine whether the absence of cognitive effects of exemestane is specific to this drug, or is a property of all AIs. A difference in cognitive effects between different AIs has potential implications for clinical practice.

With respect to tamoxifen, our results confirm our hypothesis of detrimental effects on certain cognitive domains (i.e. verbal memory and executive functioning). Based on the assumption that estrogens are beneficial for cognitive functioning, one might conclude that tamoxifen acts as an anti-estrogen on brain tissue. But, as it is questionable whether estrogens are beneficial for cognitive functioning in older women (>65 years of age)\textsuperscript{40}, one might also conclude that tamoxifen has estrogenic effects on the brain, at least in older women. So, in spite of the consistent finding of detrimental cognitive effects of tamoxifen
in studies conducted up to now, including this study, these results do not provide clues to the mechanisms of action of tamoxifen in brain tissue. Animal models might provide insight into these mechanisms of action. Potential mechanisms to evaluate in future research should include the effects of tamoxifen on the two estrogen receptors, ERα and ERβ, in the brain. Since estrogens may have different effects on ERα and ERβ\textsuperscript{41}, which are also differentially expressed in various parts of the brain\textsuperscript{42}, this distinction might be relevant for tamoxifen as well. Additionally, tamoxifen may act as an antagonist and as an agonist of ERs, or via mechanisms that are independent of genomic actions. In addition, age should be taken into account in animal studies as age is a factor of possible importance regarding the effects of endocrine treatments on the brain.

**Cognitive performance before the start of adjuvant therapy, do different statistical methods lead to different results?**

Two chapters in this thesis describe cognitive functioning before the start of endocrine treatment, each from a different point of view. In Chapter 3, methodological issues are discussed regarding, among others, the use of predefined criteria for cognitive impairment based on the number of tests failed. In Chapter 4, cognitive differences were evaluated by comparing mean cognitive scores between the breast cancer patients and the healthy controls. Although Chapter 3 focuses on methodological issues and did not aim to judge cognitive performance of breast cancer patients compared to healthy controls, one might conclude from these data that the cognitive performance of breast cancer patients was comparable to that of healthy controls, as the two groups were not significantly different with respect to the proportion of individuals who were classified as ‘cognitively impaired’. On the contrary, in Chapter 4, the results showed a statistically significantly lower overall cognitive performance of breast cancer patients compared to healthy controls.

The two studies were based on exactly the same data but revealed divergent results, demonstrating that the conclusions are dependent on the statistical method used. The extent to which methods using criteria and methods comparing mean test scores between groups will produce different results, depends on, among other factors, group size and the distribution of test scores within the group. Both types of analyses are widely used in the neuropsychological literature, separately or combined.\textsuperscript{25,43} In general, the analysis of mean cognitive scores has the advantage that the complete range of scores on a test is used without loss of information as a result of the classification. Data of proportions of
individuals with ‘cognitive impairment’ according to a particular criterion identify and highlight the individuals with the lowest scores. This might be justified in some cases, for example if there is evidence that only a specific subgroup, exclusive of the others, is cognitively affected. An important point of concern is that the compilation of such a subgroup is highly dependent on the nature and strictness of the criterion. Furthermore, the assignment of individuals to the ‘cognitively intact’ or ‘cognitively impaired’ subgroup might be influenced by confounding factors such as age, education, IQ, comorbidities etc. Therefore, it cannot be assumed that individuals in the ‘cognitively impaired’ subgroup, exclusive of the others, are actually the ones who are cognitively affected by the condition under study.

One of the aims of this thesis was to evaluate cognitive functioning of postmenopausal breast cancer patients before the start of endocrine treatment. No reason for identifying a specific subgroup of individuals exists in this situation. Therefore, comparing mean cognitive scores between patients and healthy controls, as is done in the study described in Chapter 4, is the preferred method. The study described in Chapter 3 must be considered purely as a demonstration of the impact of different criteria for cognitive impairment and different reference groups on the observed prevalence. For the aim of this study, the use of the baseline cognitive assessment data was arbitrary.

Differences between effects of chemotherapy followed by endocrine treatment and endocrine treatment only

In this thesis, two studies with a focus on cognitive functioning in patients receiving tamoxifen or exemestane are described (Chapter 5 and 6). Due to many differences, the ability to compare these studies is limited. Among others, differences exist in the design (prospective versus cross-sectional, the latter lacking the possibility to adjust for pre-treatment cognitive differences); the size of the tamoxifen, exemestane and healthy control groups (80, 99 and 120 participants versus 30, 50 and 48 participants, the smaller study having less statistical power); prior adjuvant systemic treatment (no chemotherapy versus AC-chemotherapy); the age of the participants (roughly 68 versus 58 years of age) and time since diagnosis (roughly one versus three years). Furthermore, in the cross-sectional study raw test scores were compared between groups, whereas in the prospective study cognitive domain scores were created.
Nevertheless, if the results of both studies would point in the same direction, conclusions about the cognitive effects of both tamoxifen and exemestane increase in robustness. Therefore, we exploratory compared both studies with respect to the cognitive domains in which low scores or decreased scores were observed, disregarding statistical significance. We observed that, with respect to verbal memory, both studies report larger detrimental effects of tamoxifen than of exemestane. The same is true for most tests of executive functioning and information processing speed, although for two tests (Trailmaking A and B) the results are not congruent between both studies. The results of the cross-sectional study further suggest relatively large effects on reaction speed for both treatment groups which were not observed in the prospective study. The AC-chemotherapy, speculatively, might have played a role in the low scores for reaction speed. Finally, only in the cross-sectional study was a detrimental effect on verbal fluency observed for tamoxifen users.

In summary, the results of both studies point in the same direction in that they both suggest differential effects of tamoxifen and exemestane, and suggest larger and more widespread effects of tamoxifen on cognitive functioning compared to exemestane.

**Implications for clinical practice and further developments**

*Associations between cognitive test performance and cognitive complaints, ecological validity of tests*

In the studies described in this thesis no associations were found between self-reports of cognitive functioning and cognitive test performance. Our findings confirm the findings of earlier studies in cancer patients, as well as in other patient groups. In the literature, the degree to which test performance corresponds to ‘real world’ performance (the ‘ecological validity’ of neuropsychological tests) receives increasing attention. In studies on the ecological validity of tests, associations between neuropsychological tests and outcome measures representing ‘real world performance’
Examples of these outcome measures are: self-reports, checklists, informant-based questionnaires, clinicians’ ratings, and observations of simulated activities. Demonstrating the ecological validity of tests is complex, because it is influenced by many factors. Some of these concern the person who conducts the test or provides the information for the ‘outcome measure’ (for example personality characteristics, anxiety/depression, fatigue, illness severity, age, IQ and aptitudes, individual believes about someone’s cognitive ability in different situations and the demands of the professional and social situation relative to someone’s cognitive capacities). Besides these person-related factors the ecological validity of tests is influenced by the nature of the testing environment.

A review of studies investigating the ecological validity of tests demonstrated that the magnitude of associations between neuropsychological evaluations and measures of ‘real world’ cognitive skills was in the moderate range, and many individual tests were not, or only weakly related to outcome measures. A relatively robust conclusion was that, in neurologically impaired individuals, self-reports were more weakly correlated with neuropsychological examinations than clinician and informant ratings. In a recent study investigating the ecological validity of neuropsychological examinations, the neuropsychological examination itself could predict 30% of ‘real world functioning’ (as measured by interviews in which problematic daily life activities were identified and videotapes of participants performing these problematic activities). When neuropsychologists took additional information into account, such as observations of participants performing the tests, mood and neuropsychiatric symptoms, their ability to predict ‘real world functioning’ increased by another 30%.

To conclude, ‘real world’ performance is poorly predicted by neuropsychological examinations only. The predictive value can be increased by adding information from other sources, for example mood or neuropsychiatric functioning. The use of self-reports as the only outcome measure of ‘real world’ performance has shortcomings too. Although self-reports of cognitive functioning are important in clinical practice, they are not the best outcome measures to determine the ecological validity of neuropsychological tests. In future research with cancer patients, the addition of other outcome measures may improve the ecological validity of neuropsychological examinations. For example, the outcome measure ‘return to work’ has been proved to be associated with cognitive test
performance in various patient groups. Furthermore, other outcome measures, such as observations by informants or hospital/rehabilitation professionals, or memory diaries kept by the patient might provide additional information about cognitive problems that cancer patients might face in their everyday functioning.

For health care professionals, the weak associations between self-reported cognitive complaints and cognitive test performance might complicate the choice of further diagnostics and possible interventions for patients who express cognitive complaints. Patients with cognitive complaints are, after all, not necessarily the ones who have impaired cognitive test performance. However, these weak associations are observed in studies in which patients are actively approached by researchers and interviewed about possible cognitive complaints. It is possible that spontaneous cognitive complaints expressed by a cancer patient in a clinical setting have a different meaning than complaints that consist of responses to questions in a scientific study. In future studies, it should be determined whether associations between self-reported cognitive complaints and cognitive test performance are stronger in patients who express cognitive complaints spontaneously than in patients who participate in scientific studies.

Clinical relevance of findings

When the effect of a treatment on cognitive functioning is statistically significant, this does not automatically mean that this effect is also clinically relevant. Statistical analysis in clinical research is used to show that the findings are not likely due to chance. Clinical relevance merely focuses on the meaning and implications of the effect for patients and health care professionals. Although the exact meaning of the term ‘clinical relevance’ is dependent on the focus of the study, it is generally used to describe the magnitude of the effect, the extent to which the effect interferes with the daily life of patients or the extent to which useful recommendations for intervention can be provided.

Although this thesis provides evidence for statistically significant, negative effects of tamoxifen on several cognitive functions (verbal memory, executive functioning), the clinical relevance of this finding is not immediately obvious. As stated earlier, the degree to which neuropsychological test performance corresponds to ‘real world’ performance is limited in case no additional information is used, and self-reports of cognitive functioning are not the best predictors of ‘real world’ performance. Nevertheless, our results provide
several indications of clinical relevance. First, the small-to-medium magnitudes of the observed effects are not negligible. Further indications of clinical relevance are the consistence of our findings with earlier studies with respect to the cognitive effects of tamoxifen, the consistency of the cognitive domains found to be affected in our and earlier studies and the theoretical possibility of effects of tamoxifen on the brain.

An important suggestion from our results, and so far not described in the literature, is that the effects of tamoxifen on cognitive functioning are larger and more widespread in the older patients (65 - 85 years) compared to the younger patients (50 - 65 years). If this age effect is confirmed in future studies, this might have implications for clinical practice. The elderly are most at risk for cognitive deterioration. Cancer, treatments for cancer, comorbidities and several types of drugs (such as anxiolytics, sedatives and analgesics) can independently contribute to cognitive impairment in elderly breast cancer patients.

What can be concluded so far from our data with regard to clinical practice? Given the indications for clinical relevance listed above, it is recommended to take into account the potential cognitive effects of tamoxifen in the treatment decision-making process. In order to determine the optimum choice and sequence of the available endocrine agents from both an efficacy and quality of life perspective, all benefits and side effects should be considered and carefully weighted in the context of the individual patient and her comorbid conditions.

In elderly cancer patients, cognitive assessments are recommended. Such a cognitive assessment could be part of a Comprehensive Geriatric Assessment (CGA). This is a term coined by geriatricians to describe a multidisciplinary comprehensive evaluation of an older individual’s functional status, comorbid medical conditions, cognition, psychological state, social support, nutritional status, and a review of the patient’s medications. It has been demonstrated that the domains evaluated in a CGA can predict morbidity and mortality in older patients with cancer.\textsuperscript{59-61} Incorporating a CGA in older patients at serial time points (prior to, during and after cancer treatment) can provide information regarding the short- and long-term impact of cancer therapy on cognitive functioning and other geriatric assessment variables. Other applications for the CGA, such as guiding interventions to improve the outcome in older cancer patients and the development of
novel end points for clinical trials that address quality of life and functional independence, are currently considered.62

Many questions relating to the clinical relevance of the cognitive effects of tamoxifen and exemestane remain unanswered in this thesis. For example, it is not known whether a longer duration of endocrine treatment would result in larger effects on cognitive function than the one year of treatment we investigated. Currently, two research projects have been initiated at the Netherlands Cancer Institute to evaluate the cognitive effects of a longer duration of endocrine treatment. First, all participants of the prospective study are invited for a third measurement after 4 to 5 years of endocrine treatment. With this study we will evaluate the effects of 4 to 5 years of exemestane, and the effects of 2 to 2.5 years of tamoxifen followed by 2 to 2.5 years of exemestane on cognitive functioning. Secondly, a cross-sectional study has been started to evaluate cognitive functioning in postmenopausal breast cancer patients who receive tamoxifen for at least two years. Cognitive functioning of these patients will be compared with cognitive functioning of healthy controls, as well as with cognitive functioning of breast cancer patients who have not received endocrine therapy and/or chemotherapy. This ‘breast cancer control group’ has been added in order to restrict the extent of possible pre-treatment cognitive differences between the study groups since adjustment for pre-treatment cognitive differences is impossible in cross-sectional studies. Furthermore, it is unknown whether the cognitive effects of endocrine treatment are lasting after the treatment is finished. Knowledge about the stability or reversibility of cognitive effects may have important implications for clinical practice.

Information, diagnostics and interventions for cancer patients experiencing cognitive problems

While research is ongoing to unravel the complex issues with respect to cognitive problems associated with cancer and cancer treatments, in clinical practice health care professionals are sometimes faced with patients expressing questions or concerns regarding cognitive issues. A survey of nurses working at several departments in the Antoni van Leeuwenhoek Hospital revealed that 74% of the nurses reported being aware of the occurrence of cognitive problems associated with cancer or cancer treatment, 60% ever received questions from patients regarding cognitive functioning and 63% ever gave
information to patients about cognitive functioning in relation to cancer and cancer treatments.\textsuperscript{63}

Evidence-based information, guidelines and treatments regarding cognitive functioning are scarce. There is a need for guidelines or a program in order to inform individual patients about cognitive problems associated with cancer and cancer treatment, to develop diagnostic tools to find the underlying cause(s), and determine ways for rehabilitation. Currently, at the Netherlands Cancer Institute, a short patient education program about cognitive problems related to cancer and cancer treatments is being developed. The program consists of an information pamphlet for patients and additional education for health care professionals about cognitive problems in relation to the type of treatment, time since diagnosis/treatment and possible associations with fatigue and psychosocial distress. The education program will also provide instructions for coping with complaints. In the future, specific interventions based on, among others, existing cognitive training/rehabilitation strategies for patients with brain damage and cognitive behavioral therapy for post-cancer fatigue may be helpful in improving the ability to compensate for cognitive problems.
Summary of results and general discussion

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Summary of results and general discussion

1. **Evidence on Cognitive Impact and Metabolites**
   - **Bouwens SFM.** *Ecological aspects of cognitive assessment.* Maastricht University, 2009.


Samenvatting
Samenvatting

In dit proefschrift wordt verslag gedaan van een onderzoek naar de effecten van endocriene therapie op het cognitief functioneren (zoals het geheugen en concentratie-vermogen) van postmenopauzale borstkankerpatiënten. Endocriene therapie is een belangrijke behandelingsoptie voor patiënten met hormoongevoelige borstkanker. Bij hormoongevoelige borstkanker is de tumor voor zijn groei afhankelijk van oestrogenen. Endocriene therapie werkt oestrogenen tegen door te binden aan oestrogeenreceptoren (selectieve oestrogeen receptor modulatoren, SERMs) of door de synthese van oestrogenen te remmen (aromatase remmers).

In hoofdstuk 1 wordt een introductie tot het onderzoek gegeven. De aanleiding voor een specifieke studie naar de effecten van endocriene therapie op het cognitief functioneren kan gevonden worden in de toenemende kennis over het belang van oestrogenen voor het functioneren van de hersenen en voor de cognitieve functies. Er is nog weinig bekend over de precieze werkingsmechanismen van oestrogenen in de hersenen, maar de aanwezigheid van oestrogeenreceptoren in hersendelen die van belang zijn voor het cognitief functioneren wijzen op activiteit van oestrogenen via deze receptoren. Gezien de gunstige effecten van oestrogenen op het cognitief functioneren is het theoretisch mogelijk dat endocriene therapie voor borstkanker een (mogelijk negatief) effect heeft op het cognitief functioneren. Tot nu toe is naar de effecten van endocriene therapie op de cognitieve functies weinig onderzoek gedaan.

Cognitieve problemen kunnen beperkingen met zich meebrengen in het dagelijks functioneren en de kwaliteit van leven verminderen. Deze studie heeft als doel het begrip te vergroten van de (mogelijk verschillende) effecten van de diverse endocriene therapieën op het cognitief functioneren. Daarnaast wordt aandacht geschonken aan de ervaringen van patiënten met betrekking tot dit belangrijke aspect van de kwaliteit van leven en naar de betekenis van andere factoren, zoals vermoeidheid, angst/depressie en menopauzale klachten voor het cognitief functioneren. De opgedane kennis kan gebruikt worden om patiënten en artsen van ‘evidence based’ informatie en richtsnoeren te voorzien. In de toekomst zou de kennis gebruikt kunnen worden voor de ontwikkeling van interventies voor patiënten met klachten over hun cognitief functioneren.
In 2001 startte de Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. In deze gerandomiseerde studie worden de werkzaamheid en de bijwerkingen van 2.5-3 jaar behandeling met de SERM tamoxifen, gevolgd door 2-2.5 jaar behandeling met de aromatase remmer exemestane vergeleken met 5 jaar behandeling met exemestane. Deze internationale trial had meerdere nationale substudies die zich richtten op specifieke bijwerkingen, zoals een studie naar effecten op de botdichtheid en een studie naar effecten op lipidwaarden in het bloed. De studie beschreven in dit proefschrift is de Nederlandse neuropsychologische nevenstudie van de TEAM trial. Het doel was om de effecten van tamoxifen en exemestane op de cognitieve functies te onderzoeken in de context van een gerandomiseerde studie. Het cognitief functioneren werd gemeten met gestandaardiseerde neuropsychologische tests. Het prospectieve karakter van de studie (met twee meetmomenten: voor aanvang van de endocriene therapie en na een jaar endocriene therapie) en het gebruik van diverse zelfrapportage maten voor cognitief functioneren en kwaliteit van leven maakten het mogelijk om diverse andere relevante onderwerpen te onderzoeken. Voorbeelden zijn de mogelijke aanwezigheid van cognitief disfunctioneren bij borstkankerpatiënten vóór aanvang van de endocriene behandeling, en associaties tussen zelfrapportage over het cognitief functioneren en cognitieve testprestaties en andere factoren (zoals vermoeidheid, angst/depressie en menopauzale klachten).

In hoofdstuk 2 wordt een overzicht gegevens van de literatuur die tot nu toe verschenen is over effecten van oestrogenen en endocriene therapie voor borstkanker bij postmenopauzale vrouwen. Vele studies zijn verschenen over de effecten van oestrogenen op het cognitief functioneren, maar slechts enkele over de effecten van endocriene therapie voor borstkanker. Samengevat geven deze studies aanwijzingen dat de SERM tamoxifen mogelijk negatieve effecten heeft op enkele specifieke cognitieve functies, zoals het geheugen en de snelheid van informatieverwerking. De resultaten van studies naar de cognitieve effecten van anastrozole (de enige aromatase remmer die tot nu toe is onderzocht op effecten op de cognitieve functies) zijn niet eenduidig: in enkele studies werden negatieve effecten gevonden terwijl in één studie geen enkel effect op het cognitief functioneren werd gevonden.

In de hoofdstukken 3 en 4 worden twee studies beschreven waarin gekeken is naar het cognitief functioneren voordat gestart werd met de endocriene therapie. Eén van de manieren om het cognitief functioneren te onderzoeken is door deelnemers aan de studie
te classificeren als ‘cognitief afwijkend’ of ‘cognitief normaal’ aan de hand van een vooraf bepaald criterium. Het zodoende gevonden percentage in de patiëntengroep kan vergeleken worden met het gevonden percentage in een controlegroep. In de literatuur over cognitief functioneren bij kanker worden diverse criteria gebruikt en verschillende typen controlegroepen. Dit kan resulteren in aanzienlijke verschillen in het geobserveerde percentages patiënten die geclassificeerd zijn als ‘cognitief afwijkend’. In hoofdstuk 3 hebben wij beschreven welke invloed vier verschillende criteria voor cognitieve stoornis (namelijk falen op resp. ≥4, ≥3, ≥2 en ≥1 tests) en twee typen controlegroepen (respectievelijk een door ons, specifiek voor deze studie samengestelde controlegroep en gepubliceerde normgegevens) hadden op het percentage patiënten dat als ‘cognitief afwijkend’ werd geclassificeerd. De groep patiënten bestond uit 205 postmenopauzale borstkanker patiënten (gemiddelde leeftijd 68.9 jaar) vlak voordat zij gingen starten met endocriene therapie. De studie-specifieke controlegroep bestond uit 124 postmenopauzale familieleden/vriendinnen/ kennissen van de patiënten (gemiddelde leeftijd 66.5 jaar). Uit de studie bleek, zoals verwacht, dat het percentage patiënten dat als ‘cognitief afwijkend’ werd geclassificeerd sterk varieerde met de strengheid van het criterium. Daarnaast bleek het percentage als ‘cognitief afwijkend’ geclassificeerde patiënten afhankelijk van de gekozen controlegroep. Het percentage ‘cognitief afwijkende’ patiënten varieerde op grond van gepubliceerde normgegevens van 1% voor het strengste criterium tot 36.6% voor het minst strenge criterium. In vergelijking tot de studie-specifieke normgroep varieerde het percentage van 13.7% voor het strengste criterium tot 45.5% voor het minst strenge criterium. Uit deze studie blijkt dus dat het gebruikte criterium en de gebruikte controlegroep van grote invloed zijn op het percentage patiënten dat als afwijkend wordt geclassificeerd. Daarom is het van groot belang dat er in studies naar het cognitief functioneren tijdens of na adjuvante systemische therapie consensus wordt gezocht met betrekking tot de statistische analyse methoden.

In de tweede studie (hoofdstuk 4) is gekeken welke medische en psychologische factoren geassocieerd zijn met de cognitieve testprestaties voor aanvang van adjuvante systemische therapie, en om het cognitief functioneren van de borstkankerpatiënten te vergelijken met gezonde controlepersonen, rekening houdend met medische en psychologische factoren. De gegevens van dezelfde groep patiënten (n=205, gemiddelde leeftijd 68.9 jaar) en gezonde controles (n=124, gemiddelde leeftijd 66.5 jaar) als in hoofdstuk 3 zijn gebruikt. We analyseerden de gegevens op groepsniveau. Leeftijd en IQ
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waren, zoals verwacht, sterk geassocieerd met cognitieve prestaties. Daarnaast bleken, onafhankelijk van leeftijd en IQ, ‘behandeld worden voor hoge bloeddruk’, ‘behandeld worden voor diabetes mellitus’, minder uren per dag bezig zijn met cognitief stimulerende activiteiten (zoals lezen, puzzelen), ‘minder dagen sinds de operatie’, en ‘groter aantal jaren tussen eerste menstruatie en menopauze’ geassocieerd met lagere cognitieve prestaties op één of meerdere cognitieve domeinen. Deze medische en psychologische factoren verklaarden 1-6% van de variantie boven op de 10-40% van de variantie die verklaard werd door leeftijd en IQ. Het verschil in cognitieve prestaties tussen borstkankerpatiënten en gezonde controles kon gedeeltelijk worden verklaard door de variabelen die wij onderzochten, maar een klein-tot-middelgroot verschil bleef onverklaard. Deze resultaten wijzen op het belang om in statistische analyses van cognitieve testprestaties rekening te houden met medische en psychologische verschillen tussen studiegroepen, en onderstreepen het belang van nader onderzoek naar de oorzaken van verminderd cognitief functioneren voor aanvang van een behandeling.

In hoofdstuk 5 wordt het centrale onderzoek van dit proefschrift beschreven, een prospectieve neuropsychologische studie onder borstkankerpatiënten van 38 Nederlandse ziekenhuizen. Het doel was om de effecten van twee typen endocriene therapie (tamoxifen en exemestane) op het cognitief functioneren te onderzoeken bij postmenopauzale borstkankerpatiënten die niet behandeld waren met chemotherapie. De patiënten waren deelnemers aan de TEAM trial. Zij werden gerandomiseerd tussen tamoxifen (n=80, gemiddelde leeftijd 68.7 jaar) en exemestane (n=99, gemiddelde leeftijd 68.3 jaar) na een operatie met curatieve intentie. Alle patiënten werden tweemaal onderworpen aan 18 neuropsychologische tests, namelijk voor aanvang van de endocriene behandeling (T1) en na één jaar behandeling (T2). Om rekening te kunnen houden met oefeneffecten, die inherent zijn aan het herhaaldelijk uitvoeren van neuropsychologische tests, werd een gezonde controlegroep aan het onderzoek toegevoegd. Uit de 18 tests werden 8 cognitieve domeinen gecreëerd. Op T2, rekening houdend met de cognitieve prestaties op T1, presteerden gebruiksters van exemestane niet slechter dan de gezonde controles. Tamoxifen gebruiksters daarentegen presteerden significant slechter op twee cognitieve domeinen: ‘verbaal geheugen’ en ‘executief functioneren’. In vergelijking met exemestane gebruiksters presteerden tamoxifen gebruiksters slechter op ‘informatieverwerkingsnelheid’. Alle significante verschillen hadden een kleine tot matige effectgrootte. Op de overige vijf cognitieve domeinen
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(visueel geheugen, werkgeheugen, verbale fluency, reactiesnelheid en motorische snelheid) waren geen prestatieverschillen tussen de drie groepen. Naast de analyses over de hele groep patiënten hebben we naar de jongere (≤65 jaar) en oudere (>65 jaar) patiënten apart gekeken. De effecten van tamoxifen bleken groter en omvatten meer cognitieve domeinen bij de oudere patiënten dan bij de jongere patiënten, wat suggereert dat de leeftijd van de patiënt een rol speelt bij de cognitieve effecten van tamoxifen.

In de klinische praktijk komt het vaak voor dat patiënten die endocriene therapie krijgen eerder een behandeling met chemotherapie hebben ondergaan. Uit eerder onderzoek van het Nederlands Kanker Instituut en van andere onderzoeksgroepen is bekend dat chemotherapie, afhankelijk van het toegepaste schema, geassocieerd is met een verminderd cognitief functioneren in een subgroep van patiënten. Om het cognitief functioneren van patiënten die behandeld werden met chemotherapie, gevolgd door endocriene therapie met tamoxifen of exemestane, te onderzoeken is een cross-sectioneel onderzoek uitgevoerd dat is beschreven in hoofdstuk 6. Aan deze studie deden patiënten uit de TEAM trial mee die een standaard dosering adjuvante AC-chemotherapie (doxorubicine/cyclophosphamide) hadden gehad voordat zij werden gerandomiseerd tussen tamoxifen (n=30, gemiddeld leeftijd 57.9 jaar) en exemestane (n=50, gemiddelde leeftijd 58.5 jaar). Gemiddeld gebruikten zij twee jaar endocriene therapie. Er werd ook een gezonde controlegroep toegevoegd, bestaand uit vrouwen uit de controlegroep van de prospectieve studie (zie hoofdstuk 5) die zoveel mogelijk overeenkwamen qua leeftijd en IQ (n=48, gemiddelde leeftijd 60.2 jaar). Er werd een vergelijking gemaakt van de prestaties op 18 cognitieve tests tussen de tamoxifen gebruikers en de exemestane gebruikers, en van de gehele patiëntengroep met de gezonde controlegroep. Er werden geen significante verschillende testscores gevonden tussen tamoxifen gebruikers en exemestane gebruikers. De resultaten gaven wel de suggestie dat tamoxifen geassocieerd is met een verminderd functioneren op verbale tests, terwijl er mogelijk een verband is tussen gebruik van exemestane en een lagere motorische snelheid. De gecombineerde patiëntengroep had significant lagere scores op tests voor verbale fluency en informatieverwerkingsnelheid dan de gezonde controles. Deze studie laat zien dat een behandeling bestaande uit chemotherapie gevolgd door endocriene therapie in postmenopauzale borstkankerpatiënten geassocieerd is met lagere scores op enkele cognitieve domeinen en geeft indicaties voor mogelijk verschillende cognitieve effecten van verschillende typen endocriene therapie. Geheugenklachten (gedefinieerd als een
frequentie van minimaal ‘regelmatig’) werden gerapporteerd door 28% van de AC/tamoxifen gebruiksters, 24% van de AC/exemestane gebruiksters en 6% van de gezonde controles. Er werden geen significante correlaties gevonden tussen cognitieve testprestaties en scores op een angst/depressie vragenlijst, of met een zelf-rapportagemaat voor cognitief functioneren.

De studie die beschreven wordt in hoofdstuk 7 heeft als onderwerp het cognitief functioneren zoals gerapporteerd door de patiënten zelf, zowel in een interview als op een vragenlijst. Ook werden de associaties tussen het zelfgerapporteerde cognitief functioneren en de cognitieve testprestaties onderzocht, alsmede de associaties tussen zelfgerapporteerd cognitief functioneren en angst/depressie, vermoeidheid en menopauzale klachten. De patiënten waren dezelfde als van het onderzoek beschreven in hoofdstuk 5, namelijk postmenopauzale borstkankerpatiënten die deelnamen aan de TEAM trial en geen chemotherapie hadden gehad voordat zij werden gerandomiseerd tussen tamoxifen (n=80, gemiddelde leeftijd 68.7 jaar) en exemestane (n=99, gemiddelde leeftijd 68.3 jaar). Ook de gezonde controlegroep was identiek als die beschreven in hoofdstuk 5 (n=120, gemiddelde leeftijd 66.5 jaar). Alle deelnemers werden geïnterviewd over eventuele klachten over hun geheugen- en concentratie en vulden een vragenlijst in over de frequentie van een aantal alledaagse cognitieve vergissingen. Ook vulden zij vragenlijsten in over angst/depressie, vermoeidheid en menopauzale klachten, en voerden zij cognitieve tests uit. Zij deden dit tweemaal: eenmaal voor aanvang van de endocriene behandeling (T1) en eenmaal na een jaar behandeling (T2). De resultaten lieten zien dat het percentage deelnemers dat geheugenklachten rapporteerde op T2, rekening houdend met het percentage op T1, niet verschilt tussen de groepen. Voor wat betreft concentratieklachten waren de verschillen tussen de groepen wel significant: er was een toename van het aantal patiënten in de tamoxifen groep die klachten rapporteerde. Er was geen verschil tussen de groepen voor wat betreft de gerapporteerde frequentie van alledaagse cognitieve vergissingen op T2, rekening houden met de scores op T1. Dit suggereert dat ‘cognitieve klachten’ en ‘de frequentie van cognitieve vergissingen’ verschillende aspecten van het zelfgerapporteerde cognitief functioneren zijn. Er werden geen significante correlaties gevonden tussen prestaties op cognitieve tests en zelfgerapporteerd cognitief functioneren. De prestaties op cognitieve tests waren zwak, maar significant, geassocieerd met angst/depressie en vermoeidheid. De associaties tussen zelfgerapporteerd cognitief functioneren en resp. angst/depressie, vermoeidheid

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en menopauzale klachten waren matig. De resultaten van deze studie impliceren dat gebruik van tamoxifen, maar niet exemestane, geassocieerd is met een toename van klachten over het concentratievermogen. Verder blijkt uit dit onderzoek dat zelf-rapportagematen voor het cognitief functioneren niet kunnen worden gebruikt als substituut voor cognitieve tests.

Het laatste hoofdstuk, hoofdstuk 8, bevat allereerst een samenvatting van de doelen en belangrijkste bevindingen en stelt vervolgens de sterkere en zwakkere punten van de onderzoeksmethoden ter discussie. Als zwakkere punten kunnen genoemd worden de minder dan optimale participatie van patiënten die wel in aanmerking kwamen voor deelname (62% in de prospectieve studie) en de kleine groepen patiënten (met name in de cross-sectionele studie: 30 tamoxifen gebruiksters en 50 exemestane gebruiksters). Over de gezonde controlegroep kan het volgende worden opgemerkt: er is in dit onderzoek om sociodemografische verschillen zo klein mogelijk te houden gekozen voor een gezonde controlegroep bestaande uit vriendinnen en familieleden van de patiënten. Echter, de controlegroep bleek op belangrijke (medische en psychologische) factoren enigszins te verschillen van de patiëntengroep. Deze factoren bleken ook van invloed op het cognitief functioneren, zodat een statistische correctie voor cognitieve verschillen tussen de patiëntengroepen en de controlegroep moest worden uitgevoerd. Tegenover deze zwakkere punten staan enkele duidelijk sterke punten, zoals het prospectieve karakter van de studie, de uitgebreide neuropsychologische testbatterij met diverse zelfrapportagematen, de keuze van de cognitieve domeinen en de gerandomiseerde toewijzing van patiënten aan tamoxifen of exemestane.

Hoe kunnen de verschillen die we vonden tussen de cognitieve effecten van tamoxifen en exemestane worden verklaard? Op basis van wat bekend is over de werking-mechanismen van beide middelen en de schaarse literatuur over de effecten op het cognitief functioneren werd als hypothese gesteld dat beide middelen een negatief effect op het cognitief functioneren zouden hebben. Voor wat betreft tamoxifen werd dat ook gevonden, maar niet voor exemestane. De verlaging van oestrogeenwaarden door exemestane uitte zich niet in een meetbare achteruitgang voor het cognitief functioneren. Als mogelijke verklaring zou gedacht kunnen worden aan de licht androgene werking van exemestane. Androgenen kunnen ook van invloed zijn op de cognitieve functies en zouden de negatieve invloed van de oestrogeendaling op het cognitief functioneren kunnen verminderen of voorkomen. Of dit laatste het geval is zou in de toekomst kunnen worden
bekeken in een studie waarin de cognitieve effecten van exemestane worden vergeleken met andere aromatase remmers zonder androgene werking, zoals anastrozole en letrozole. Hoewel de cognitieve effecten die we vonden bij tamoxifen in dezelfde lijn liggen als de bevindingen in eerdere studies, is weinig bekend over de werkingsmechanismen van tamoxifen in de hersenen. Deze mechanismen zouden verder onderzocht kunnen worden in dierstudies.

Verder wordt ingegaan op de verschillen in doelen en methoden van de twee studies naar het cognitief functioneren voor aanvang van de endocriene therapie (hoofdstuk 3 en 4), en worden de twee studies waarin cognitieve effecten van tamoxifen en exemestane worden beschreven (hoofdstuk 5 en 6) vergeleken.

Ten slotte wordt ingegaan op de implicaties van onze onderzoeksresultaten voor de klinische praktijk en voor toekomstig onderzoek. Allereerst wordt stilgestaan bij het feit dat in deze studie, net zoals in vele andere neuropsychologische studies, cognitieve testprestaties niet gerelateerd waren aan wat patiënten zelf rapporterden over hun cognitief functioneren. Enerzijds betekent dit dat cognitieve tests niet vervangen kunnen worden door dat zelfrapportage schalen in onderzoek naar de effecten van anticancertrente behandelingen op het cognitief functioneren. Anderzijds betekent dit dat de informatie uit de cognitieve tests niet voldoende is om de problemen zoals patiënten deze ervaren te voorspellen.

Hoewel enkele in deze studie gevonden effecten van tamoxifen op het cognitief functioneren statistisch significant zijn, betekent dit nog niet direct dat zij ook klinisch relevant zijn. Toch bieden de onderzoeksresultaten aanwijzingen voor klinische relevantie. De effectgroottes van de cognitieve verschillen zijn klein tot matig, maar daarom niet te verwaarlozen. Ook zijn de resultaten conform de bestaande literatuur en zijn effecten van tamoxifen op de hersenen theoretisch mogelijk. Onze bevinding dat de effecten van tamoxifen op het cognitief functioneren sterker en omvangrijker zijn bij oudere (>65 jaar) dan bij jongere (≤65 jaar) patiënten is nog niet eerder beschreven in de literatuur. Als deze bevinding in toekomstig onderzoek wordt gerepliceerd, zou dit belangrijke implicaties kunnen hebben voor de klinische praktijk, aangezien ouderen in het algemeen een hoger risico hebben op cognitieve achteruitgang dan jongeren. Kanker, antikankertrente behandelingen, comorbiditeit en diverse soorten medicatie (zoals anxiolytica, analgetica en sedativa) kunnen onafhankelijk bijdragen aan cognitieve achteruitgang in patiënten.
Gezien de door ons gevonden aanwijzingen voor klinische relevantie wordt het aanbevolen om mogelijke effecten op het cognitief functioneren mee te wegen bij het bepalen van het type en de volgorde van endocriene behandeling.

Dit onderzoek laat nog vele vragen aangaande de effecten van endocriene therapie op het cognitief functioneren onbeantwoord. Zo is nog niet bekend in hoeverre een langere behandelingsduur leidt tot grotere effecten op het cognitief functioneren. Ook is niet bekend in hoeverre de effecten op de cognitieve functies omkeerbaar zijn na het staken van de endocriene behandeling. Nadere kennis hierover kan belangrijke implicaties hebben voor de klinische praktijk.

In de klinische praktijk worden artsen en verpleegkundigen regelmatig geconfronteerd met patiënten die vragen hebben of klachten uiten over hun cognitief functioneren. Een recent onderzoek in het Antoni van Leeuwenhoekziekenhuis onder verpleegkundigen liet zien dat 60% van de verpleegkundigen wel eens vragen van patiënten heeft gekregen over het cognitief functioneren. ‘Evidence-based’ informatie en richtlijnen voor artsen en patiënten zijn echter schaars. Momenteel wordt er gewerkt aan een informatiefolder voor patiënten en een bijscholingsprogramma voor verpleegkundigen en artsen. De kennis die in de afgelopen jaren over kanker en cognitie in het Nederlands Kanker Instituut en elders in de wereld is verzameld zal hiervoor de basis vormen.
Dankwoord
Dankwoord

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About the author
About the author

Curriculum vitae

Christien Schilder was born on December 29, 1966 in Swalmen, The Netherlands. In 1985 she graduated from secondary school (VWO) at the ‘Katholieke Scholengemeenschap de Breul’ in Zeist. In that year she started with the study Human Movement Sciences at the Free University in Amsterdam. From 1989 she combined this study with the study Psychology, main subject Neuropsychology, also at the Free University. In 1990 she graduated from the study Human Movement Sciences. In 1991 she did her internship Clinical Neuropsychology at the Free University Medical Center in Amsterdam and graduated from the study Psychology in 1992. After working as a psychomotor therapist in nursing home ‘Oostergouw’ in Zaandam for the period of one year, she worked from 1993 to 2001 as a Neuropsychologist at the mental health clinic ‘GGZ InGeest’ in Amsterdam. From 1998, she combined this job with a position as a Neuropsychologist at the Mental Health Clinic ‘GGZ Noord-Holland Noord’ in Heiloo. In 2000 she was registered as a Health Care Psychologist. From 2001 to 2003, she worked as a Health Care Psychologist for an ambulant team for care for dementia patients (DOC-team) in Alkmaar. In June 2003 she started at the Netherlands Cancer Institute in Amsterdam her PhD-project, resulting in the present thesis. From 2009, she also works on a continuation of this research project. In 2010 she expects to be registered as a Clinical Neuropsychologist.
List of publications

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