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

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Publication date
2010

[Link to publication](#)

Citation for published version (APA):

Schilder, C. M. T. (2010). *Effects of tamoxifen and exemestane on cognitive functioning: a study in postmenopausal breast cancer patients*. [Thesis, fully internal, Universiteit van Amsterdam].

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Chapter 2

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

Updated and adapted from:

- Schilder CM, Schagen SB. Effects of hormonal therapy on cognitive functioning in breast cancer patients: a review of the literature. *Minerva Ginecologica* 2007;59:387-401
- Schilder CM, van Dam FS, Schagen SB. Effects of hormones and hormonal treatment on cognition. In: Meyers CA, Perry JR, eds. *Cognition and Cancer*. Cambridge: Cambridge University Press, 2008
- Schilder CM, Linn SC, van Dam FS, Schagen SB. De invloed van hormonale therapie op het cognitief functioneren van patiënten met het mammacarcinoom. *Nederlands Tijdschrift voor Geneeskunde* 2008; 52:494-498

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.⁵ In addition, there is increasing evidence that estrogens play a role in central nervous system functioning.⁶ Preclinical neuroscientific studies indicate that estrogens exert neurotrophic and neuroprotective actions in the brain.⁷ 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.^{8,9} 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.^{8,10} Other proposed beneficial effects are protection of the brain against ischemic damage by exerting anti-inflammatory actions after ischemic injury^{7,11}, promoting survival of brain cells⁷ and increasing cerebral blood flow and glucose transport into the brain.¹²

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.¹³ In contrast, other cognitive functions, such as vocabulary and other aspects of intelligence are relatively stable and show only minor decline with aging.¹⁴ 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 functioning¹⁵⁻¹⁸ or, at the most, weak effects on particular cognitive domains, i.e. memory¹⁹, information processing speed^{20,21} or verbal fluency²² 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 tasks²⁸⁻³⁰, 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 identified mixed associations, depending on the evaluated cognitive domain²⁸, 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.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.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.⁴² Several reviews^{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.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.⁴⁶ 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).⁴⁷

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.⁴⁸ 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.^{49,50}

Six neuropsychological studies included tamoxifen users. Paganini-Hill and Clark⁴⁶ 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.⁴⁷ and Eberling et al.⁵¹ used several neuropsychological tests in addition to neuro-imaging techniques (a screening instrument and tests for psychomotor speed⁴⁷, object naming, attention span, verbal memory, and pattern recognition⁵¹) 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.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.⁵³ The second study⁵⁴ 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.⁵⁵ 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.^{56,57} Moreover, raloxifene in a dose 120 mg/day (but not 60 mg/day) resulted in a reduced risk of cognitive impairment.⁵⁸

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.⁵⁹

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).⁶⁰ Consequently, aromatase inhibitors lower the level of circulating estrogen by almost 100%.⁶¹ 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.⁶² 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.

Table 1. Overview of studies on the effects of endocrine treatments for postmenopausal women on cognitive functioning

Authors	Design	Participants	Measures	Conclusions
Nickelsen <i>et al.</i> (1999) ⁵⁶	Prospective design Measurements before treatment and at 1, 6 and 12 months	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)	Memory Assessment Clinics battery Walter reed performance battery Geriatric depression scale	RAL did not impair cognitive functioning and did not affect mood in postmenopausal women treated for 1 year.
Paganini-Hill & Clark (2000) ⁴⁶	Cross-sectional design	Breast cancer patients - past TAM users (short term: <4 yrs; standard term: 4-5 yrs; long term: 6+ yrs) (N=428; mean age 69 years) - current TAM users (short term: <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)	Clock drawing task Copying a box drawing Narrative writing to describe a pictured scene. Geriatric Depression Scale Questions about memory problems	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.
Yaffe <i>et al.</i> (2001) ⁵⁷	Prospective design Measurements before treatment and at 6 months, 1, 2 and 3 years	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)	Short blessed test Trailmaking A&B Word list memory Word list fluency	RAL treatment for 3 years did not affect overall cognitive scores in postmenopausal women.
Ernst <i>et al.</i> (2002) ⁴⁷	Cross-sectional design Comparisons of mean score per test	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)	Modified MMSE Digit Symbol substitution test Trailmaking A	No differences in scores on cognitive tests.

Table 1 (continued). Overview of studies on the effects of endocrine treatments for postmenopausal women on cognitive functioning

Authors	Design	Participants	Measures	Conclusions
Jenkins <i>et al.</i> (2004) ⁵²	Cross-sectional design Group comparisons Correlational analyses between cognitive measures and depression measures, and between length of treatment and cognitive performance	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)	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	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.
Eberling <i>et al.</i> (2004) ⁵¹	Cross-sectional design Cognitive scores: comparison of group means.	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)	- Mini Mental State Examination - Verbal episodic memory - Semantic memory (object naming) - Verbal attention span - Pattern recognition Center for Epidemiologic Studies – Depression Scale	TAM users had significantly poorer scores on a semantic memory test than the other groups
Yaffe <i>et al.</i> (2005) ⁵⁸	Patients out of the Yaffe <i>et al.</i> 2001 study that scored in the lowest 10 th percentile on cognitive screening, or had clinical signs of dementia, were evaluated by a blinded dementia specialist to evaluate dementia etiology.	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	Short blessed test Evaluation by a dementia specialist Brain scans Laboratory tests	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.

Table 1 (continued). Overview of studies on the effects of endocrine treatments for postmenopausal women on cognitive functioning

Authors	Design	Participants	Measures	Conclusions
Bender <i>et al.</i> (2007) ⁵³	Cross-sectional design	Breast cancer patients, 2 groups: - TAM users (n=16; mean age 48.2 years) - ANA users (n=15; mean age 57.4 years)	Digit span, Digit vigilance test, Trailmaking A&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	Women on ANA had significantly more severe impairment than women on TAM on tests for: - visual learning and memory - verbal learning and memory
Jenkins <i>et al.</i> (2008) ⁶²	Prospective design; Measurements before the start of treatment and at 6 months and 24 months	Women at high risk for breast cancer, randomized between: - anastrozole (n=77; mean age 57 years) - placebo (n=74; mean age 57 years)	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	Anastrozole use was not associated with cognitive impairment compared with placebo

Table 1 (continued). Overview of studies on the effects of endocrine treatments for postmenopausal women on cognitive functioning

Authors	Design	Participants	Measures	Conclusions
Collins et al. (2009) ⁵⁴	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) ⁵⁹	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 = raloxifene; PL = placebo; TAM = tamoxifen; HRT = Hormone replacement therapy; CON = control; 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.⁶³ As it is known that androgens might provide benefits on performance in several cognitive domains⁶⁴, 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.¹³ 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.^{46,47,51-53} 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^{52-54,62} while others used extensive batteries of tests covering multiple cognitive domains.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.^{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.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.^{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.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.^{46,52,62} 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.⁶⁸ 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.

Reference List

- (1) Dowsett M, Cuzick J, Ingle J et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28:509-518.
- (2) Monnier A. Clinical management of adverse events in adjuvant therapy for hormone-responsive early breast cancer. *Ann Oncol*. 2007;18 Suppl 8:viii36-viii44.
- (3) Perez EA. Safety profiles of tamoxifen and the aromatase inhibitors in adjuvant therapy of hormone-responsive early breast cancer. *Ann Oncol*. 2008;18(Supplement 8):viii26-viii35.
- (4) Tralongo P, Dimari A, Repetto L. Aromatase inhibitors and mental function. *J Am Geriatr Soc*. 2005;53:166.
- (5) Deroo BJ, Korach KS. Estrogen receptors and human disease. *J Clin Invest*. 2006;116:561-570.
- (6) Sherwin BB. Estrogen and cognitive aging in women. *Neuroscience*. 2006;138:1021-1026.
- (7) Wise PM. Estrogen therapy: does it help or hurt the adult and aging brain? Insights derived from animal models. *Neuroscience*. 2006;138:831-835.
- (8) Norbury R, Cutter WJ, Compton J et al. The neuroprotective effects of estrogen on the aging brain. *Exp Gerontol*. 2003;38:109-117.
- (9) Henderson VW. Estrogen-containing hormone therapy and Alzheimer's disease risk: understanding discrepant inferences from observational and experimental research. *Neuroscience*. 2006;138:1031-1039.
- (10) Cholerton B, Gleason CE, Baker LD, Asthana S. Estrogen and Alzheimer's disease: the story so far. *Drugs Aging*. 2002;19:405-427.
- (11) Suzuki S, Brown CM, Dela Cruz CD, Yang E, Bridwell DA, Wise PM. Timing of estrogen therapy after ovariectomy dictates the efficacy of its neuroprotective and antiinflammatory actions. *Proc Natl Acad Sci U S A*. 2007;104:6013-6018.
- (12) Cheng CM, Cohen M, Wang J, Bondy CA. Estrogen augments glucose transporter and IGF1 expression in primate cerebral cortex. *FASEB J*. 2001;15:907-915.
- (13) Sherwin BB. Does estrogen protect against cognitive aging in women? *Current directions in psychological science*. 2007;16:275-279.
- (14) Dik M. *Cognitive decline in older persons; Contribution of genetics, health, and lifestyle*. Amsterdam: Free University, 2002.
- (15) Meyer PM, Powell LH, Wilson RS et al. A population-based longitudinal study of cognitive functioning in the menopausal transition. *Neurology*. 2003;61:801-806.
- (16) Henderson VW, Guthrie JR, Dudley EC, Burger HG, Dennerstein L. Estrogen exposures and memory at midlife: a population-based study of women. *Neurology*. 2003;60:1369-1371.
- (17) Weber M, Mapstone M. Memory complaints and memory performance in the menopausal transition. *Menopause*. 2009;16:694-700.
- (18) Herlitz A, Thilers P, Habib R. Endogenous estrogen is not associated with cognitive performance before, during, or after menopause. *Menopause*. 2007;14:425-431.
- (19) Greendale GA, Huang MH, Wight RG et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. *Neurology*. 2009;72:1850-1857.
- (20) Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol*. 2004;26:955-969.
- (21) Kok HS, Kuh D, Cooper R et al. Cognitive function across the life course and the menopausal transition in a British birth cohort. *Menopause*. 2006;13:19-27.
- (22) Fuh JL, Wang SJ, Lee SJ, Lu SR, Juang KD. A longitudinal study of cognition change during early menopausal transition in a rural community. *Maturitas*. 2006;53:447-453.

- (23) Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology*. 1988;13:345-357.
- (24) Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology*. 1992;17:485-495.
- (25) Verghese J, Kuslansky G, Katz MJ et al. Cognitive performance in surgically menopausal women on estrogen. *Neurology*. 2000;55:872-874.
- (26) Farrag AK, Khedr EM, Abdel-Aleem H, Rageh TA. Effect of surgical menopause on cognitive functions. *Dement Geriatr Cogn Disord*. 2002;13:193-198.
- (27) Rocca WA, Bower JH, Maraganore DM et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology*. 2007;69:1074-1083.
- (28) Drake EB, Henderson VW, Stanczyk FZ et al. Associations between circulating sex steroid hormones and cognition in normal elderly women. *Neurology*. 2000;54:599-603.
- (29) Wolf OT, Kirschbaum C. Endogenous estradiol and testosterone levels are associated with cognitive performance in older women and men. *Horm Behav*. 2002;41:259-266.
- (30) Hogervorst E, De Jager C, Budge M, Smith AD. Serum levels of estradiol and testosterone and performance in different cognitive domains in healthy elderly men and women. *Psychoneuroendocrinology*. 2004;29:405-421.
- (31) Lebrun CE, van der Schouw YT, de Jong FH, Pols HA, Grobbee DE, Lamberts SW. Endogenous oestrogens are related to cognition in healthy elderly women. *Clin Endocrinol (Oxf)*. 2005;63:50-55.
- (32) den Heijer T, Geerlings MI, Hofman A et al. Higher estrogen levels are not associated with larger hippocampi and better memory performance. *Arch Neurol*. 2003;60:213-220.
- (33) Laughlin GA, Kritz-Silverstein D, Barrett-Connor E. Endogenous oestrogens predict 4-year decline in verbal fluency in postmenopausal women: the Rancho Bernardo Study. *Clin Endocrinol (Oxf)*. 2010;72:99-106.
- (34) Barrett-Connor E, Goodman-Gruen D. Cognitive function and endogenous sex hormones in older women. *J Am Geriatr Soc*. 1999;47:1289-1293.
- (35) Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA*. 1998;279:688-695.
- (36) LeBlanc ES, Janowsky J, Chan BK, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA*. 2001;285:1489-1499.
- (37) Hogervorst E, Williams J, Budge M, Riedel W, Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. *Neuroscience*. 2000;101:485-512.
- (38) Rapp SR, Espeland MA, Shumaker SA et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289:2663-2672.
- (39) Shumaker SA, Legault C, Rapp SR et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289:2651-2662.
- (40) Espeland MA, Rapp SR, Shumaker SA et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2959-2968.
- (41) Shumaker SA, Legault C, Kuller L et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2947-2958.
- (42) Sherwin BB. Estrogen and memory in women: how can we reconcile the findings? *Horm Behav*. 2005;47:371-375.

- (43) Sherwin BB. Estrogen therapy: is time of initiation critical for neuroprotection? *Nat Rev Endocrinol.* 2009;5:620-627.
- (44) Maki PM. A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. *Ann N Y Acad Sci.* 2005;1052:182-197.
- (45) Ryan J, Carriere I, Scali J et al. Characteristics of hormone therapy, cognitive function, and dementia: the prospective 3C Study. *Neurology.* 2009;73:1729-1737.
- (46) Paganini-Hill A, Clark LJ. Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. *Breast Cancer Res Treat.* 2000;64:165-176.
- (47) Ernst T, Chang L, Cooray D et al. The effects of tamoxifen and estrogen on brain metabolism in elderly women. *J Natl Cancer Inst.* 2002;94:592-597.
- (48) Benson JR. Re: The effects of tamoxifen and estrogen on brain metabolism in elderly women. *J Natl Cancer Inst.* 2002;94:1336-1337.
- (49) Chen D, Wu CF, Shi B, Xu YM. Tamoxifen and toremifene cause impairment of learning and memory function in mice. *Pharmacol Biochem Behav.* 2002;71:269-276.
- (50) Chen D, Wu CF, Shi B, Xu YM. Tamoxifen and toremifene impair retrieval, but not acquisition, of spatial information processing in mice. *Pharmacol Biochem Behav.* 2002;72:417-421.
- (51) Eberling JL, Wu C, Tong-Turnbeaugh R, Jagust WJ. Estrogen- and tamoxifen-associated effects on brain structure and function. *Neuroimage.* 2004;21:364-371.
- (52) Jenkins V, Shilling V, Fallowfield L, Howell A, Hutton S. Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. *Psychooncology.* 2004;13:61-66.
- (53) Bender CM, Sereika SM, Brufsky AM et al. Memory impairments with adjuvant anastrozole versus tamoxifen in women with early-stage breast cancer. *Menopause.* 2007;14:995-998.
- (54) Collins B, Mackenzie J, Stewart A, Bielajew C, Verma S. Cognitive effects of hormonal therapy in early stage breast cancer patients: a prospective study. *Psychooncology.* 2009;18:811-821.
- (55) Visvanathan K, Chlebowski RT, Hurley P et al. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. *J Clin Oncol.* 2009;27:3235-3258.
- (56) Nickelsen T, Lufkin EG, Riggs BL, Cox DA, Crook TH. Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in postmenopausal women. *Psychoneuroendocrinology.* 1999;24:115-128.
- (57) Yaffe K, Krueger K, Sarkar S et al. Cognitive function in postmenopausal women treated with raloxifene. *N Engl J Med.* 2001;344:1207-1213.
- (58) Yaffe K, Krueger K, Cummings SR et al. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. *Am J Psychiatry.* 2005;162:683-690.
- (59) Legault C, Maki PM, Resnick SM et al. Effects of tamoxifen and raloxifene on memory and other cognitive abilities: cognition in the study of tamoxifen and raloxifene. *J Clin Oncol.* 2009;27:5144-5152.
- (60) Visvanathan K, Davidson NE. Aromatase inhibitors as adjuvant therapy in breast cancer. *Oncology (Huntingt).* 2003;17:335-42, 347.
- (61) Simpson ER, Dowsett M. Aromatase and its inhibitors: significance for breast cancer therapy. *Recent Prog Horm Res.* 2002;57:317-338.
- (62) Jenkins VA, Ambrosine LM, Atkins L, Cuzick J, Howell A, Fallowfield LJ. Effects of anastrozole on cognitive performance in postmenopausal women: a randomised, double-blind chemoprevention trial (IBIS II). *Lancet Oncol.* 2008;9:953-961.

- (63) Ariazi EA, Leitao A, Oprea TI et al. Exemestane's 17-hydroxylated metabolite exerts biological effects as an androgen. *Mol Cancer Ther.* 2007;6:2817-2827.
- (64) Hirshman E, Merritt P, Wang CC et al. Evidence that androgenic and estrogenic metabolites contribute to the effects of dehydroepiandrosterone on cognition in postmenopausal women. *Horm Behav.* 2004;45:144-155.
- (65) Hogervorst E, Yaffe K, Richards M, Huppert F. Hormone replacement therapy for cognitive function in postmenopausal women. *Cochrane Database Syst Rev.* 2002;CD003122.
- (66) Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. *Ann Intern Med.* 2000;133:455-463.
- (67) Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: a review on the literature on everyday cognitive skills. *Neuropsychology Review.* 2003;13:181-197.
- (68) Jenkins V, Atkins L, Fallowfield L. Does endocrine therapy for the treatment and prevention of breast cancer affect memory and cognition? *Eur J Cancer.* 2007;43:1342-1347.