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

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Publication date
2010

Chapter 7

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

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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[1,5,9-11], 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[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.[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[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 *self-reported* by users of endocrine treatment.

The first aim of the present analysis was to evaluate *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.

Patients and Methods

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

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.[29] 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).[30] 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.[30] 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.[10,31,32] Secondly, the *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.[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.[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.[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.[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.

Cognitive tests

Cognitive functioning was assessed by a comprehensive test battery, existing of 18 test indices covering the cognitive domains of *verbal memory* (Rey auditory verbal memory test: immediate and delayed recall, Visual association test), *visual memory* (WMS visual memory: immediate and delayed recall[38]), *information processing speed* (Trailmaking A[39], Stroop Card 1 and 2[40]), *executive functioning* (Trailmaking B[39], Stroop Card 3[40]), *working memory* (WAIS-III Letter-number sequencing[41]), *reaction speed* (FePsy Visual reaction times: dominant and non-dominant hand[42]), *motor speed* (FePsy Finger Tapping: dominant and non-dominant hand[42]) and *verbal fluency* (Categories animals and professions[43],

Letterfluency[44]). Tests were selected for reliability, validity, sensitivity for effects of hormones and suitability for older age groups. The Dutch Adult Reading Test[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 χ^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 items 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 α (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.[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.

Results

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*=<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.

Table 1. Sociodemographics of the tamoxifen users, the exemestane users and the healthy controls

	Tamoxifen users (n=80)	**Exemestane users (n=99)**	**Healthy controls (n=120)**	**p-value[a]**
Age; Mean (SD)	68.7 (7.6) Range 51-84	68.3 (6.8) Range 50-82	66.2 (7.9) Range 49-86	0.03[b]
IQ; Mean (SD)	100.7 (20.0)	100.5 (18.6)	105.8 (19.0)	0.07
T1-T2 interval in months; Mean (SD)	12.4 (1.2)	12.2 (1.4)	12.3 (0.6)	0.25
Underwent Radiotherapy; % (n)	58.8 (47)	68.7 (68)	-	0.16
Ever-use of hormone replacement therapy % (n)	17.5 (14)	20.2 (20)	19.2 (23)	0.79

[a]P-values for ANOVA (for age, IQ and T1-T2 interval) and χ^2 test (for 'self-reported adherence',' T1-T2 interval' and 'underwent radiotherapy').
[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

	Internal consistency at T1 (Cronbach's α)	**Internal consistency at T2 (Cronbach's α)**	**Correlation T1-T2 Pearson's r.**
Cognitive interview-scale[a]	0.52	0.52	0.56
CFQ[b]	0.88	0.90	0.76
HSCL[c]	0.89	0.89	0.58
EORTC QLQ-C30 fatigue scale[d]	0.78	0.81	0.57
FACT-B ES[e]	0.70	0.76	0.67

[a]Self-composed scale out of two questions regarding memory and concentration complaints.
[b]Cognitive failures questionnaire.
[c]Hopkins Symptom Check List.
[d]European Organization for Research and Treatment of Cancer Quality of Life questionnaire.
[e]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

	Baseline (T1)				**Follow-up (T2)**			
	Tamoxifen users (n=80)	**Exemestane users (n=99)**	**Healthy controls (n=120)**	***P****	**Tamoxifen users (n=80)**	**Exemestane users (n=99)**	**Healthy controls (n=120)**	***P*** **
Memory complaints[a] % (n)	45 (36)	38 (38)	38 (46)	0.23	54 (43)	47 (46)	41 (49)	0.09
Forgetting appointments[a]	*10 (8)*	*3 (3)*	*5 (6)*	*0.31*	*14 (11)*	*10 (10)*	*5 (6)*	0.06
Losing one's things[a]	*21 (17)*	*16 (16)*	*12 (14)*	*0.04*	*17 (13)*	*15 (15)*	*10 (12)*	0.64
Forgetting telephone numbers[a]	*11 (9)*	*10 (10)*	*7 (8)*	*0.25*	*14 (11)*	*6 (6)*	*5 (6)*	0.12
Concentration complaints[a]; % (n)	26 (21)	24 (24)	34 (41)	0.48	48 (38)	27 (27)	32 (38)	0.003
Distractibility[a]	*20 (16)*	*16 (16)*	*24 (29)*	*0.68*	*31 (25)*	*18 (18)*	*23 (27)*	0.03
Problems with sustained attention[a]	*16 (13)*	*8 (8)*	*14 (17)*	*0.66*	*33 (26)*	*16 (16)*	*18 (22)*	0.02
Problems with multitasking[a]	*14 (11)*	*9 (9)*	*8 (10)*	*0.12*	*15 (12)*	*9 (9)*	*5 (6)*	0.04
Cognitive Interview-scale[b]; mean (SD)	.71 (.83)	.63 (.71)	.73 (.80)	0.74	1.0 (.82)	.74 (.79)	.73 (.79)	0.009
CFQ[c]; mean (SD)	31 (11)	28 (11)	33 (8)	0.004	31 (12)	28 (11)	32 (9)	0.54

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

[a]Percentage of participants expressing a complaint.

[b]Scale based on two interview questions (see Method section); range 0-2; higher score means more complaints.

[c]CFQ; 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

	Baseline (T1)			**P***	**Follow-up (T2)**			**P****
	Tamoxifen users (n=80)	**Exemestane users (n=99)**	**Healthy controls (n=120)**		**Tamoxifen users (n=80)**	**Exemestane users (n=99)**	**Healthy controls (n=120)**	
Anxiety/Depression[a]; mean (SD)	14 (11)	12 (11)	10 (9)	0.08	17 (15)	15 (12)	13 (9)	0.54
- possible depressive case[b]; % (n)	27 (22)	20 (20)	14 (17)	0.03	35 (28)	34 (34)	22 (27)	0.57
Fatigue[c]; mean (SD)	34 (22)	32 (22)	18 (16)	<0.001	30 (24)	27 (21)	22 (18)	0.29
Menopausal complaints[d]; mean (SD)	62 (7)	63 (6)	63 (6)	0.14	60 (8)	62 (7)	64 (6)	<0.001

*P-value of ANOVA; **P-value of ANCOVA, using the score at T1 as a covariate.

[a]HSCL; range 0-100, higher score means more serious symptoms.

[b]'Possible depressive case' defined as a mean HSCL item-score of ≥1.55.

[c]EORTC QLQ-C30 fatigue subscale; range 0-100, higher score means more serious symptoms.

[d]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

	Baseline (T1)					Follow-up (T2)				
	Cognitive failures[b]	**Fatigue[c]**	**Anxiety depression[d]**	**Menopausal complaints[e]**	**Cognitive test per-formance[f]**	**Cognitive failures[b]**	**Fatigue[c]**	**Anxiety/ Depression[d]**	**Menopausal complaints[e]**	**Cognitive test per-formance[f]**
Cognitive complaints[a]	0.29**	0.15*	0.21**	-0.11	-0.04	0.32**	0.30**	0.33**	-0.23**	-0.09
Cognitive failures[b]		0.11	0.22**	-0.20**	-0.01		0.23**	0.31**	-0.27**	-0.05
Fatigue[c]			0.51**	-0.35**	-0.14*			0.48**	-0.42**	-0.17**
Anxiety/ depression[d]				-0.45**	-0.13*				-0.45**	-0.19**
Menopausal complaints[e]					0.09					-0.06

*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.[46] 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[47] and in healthy older adults[16], 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.[27] 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.[47] 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.[26] 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.[3] 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[1,48] and the construction of self-report measures being a more valid representation of cognitive functioning[19] 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[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.[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[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.[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.[26,50] It is also

known that cognitive complaints might be associated with feelings of anxiety, depression and/or fatigue. [1,48] 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.

Reference List

(1) Shilling V, Jenkins V. Self-reported cognitive problems in women receiving adjuvant therapy for breast cancer. *Eur J Oncol Nurs.* 2007;11:6-15.
(2) Debess J, Riis JO, Pedersen L, Ewertz M. Cognitive function and quality of life after surgery for early breast cancer in North Jutland, Denmark. *Acta Oncol.* 2009;48:532-540.
(3) Pullens MJ, De Vries J, Roukema JA. Subjective cognitive dysfunction in breast cancer patients: a systematic review. *Psychooncology.* 2009; Dec 17, e-pub ahead of print.
(4) Schagen SB, Das E, van Dam FS. The influence of priming and pre-existing knowledge of chemotherapy-associated cognitive complaints on the reporting of such complaints in breast cancer patients. *Psychooncology.* 2009;18:674-678.
(5) Weis J, Poppelreuter M, Bartsch HH. Cognitive deficits as long-term side-effects of adjuvant therapy in breast cancer patients: 'subjective' complaints and 'objective' neuropsychological test results. *Psychooncology.* 2009;18:775-782.
(6) Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. *Int J Geriatr Psychiatry.* 2000;15:983-991.
(7) Westoby CJ, Mallen CD, Thomas E. Cognitive complaints in a general population of older adults: prevalence, association with pain and the influence of concurrent affective disorders. *Eur J Pain.* 2009;13:970-976.
(8) Tannock IF, Ahles TA, Ganz PA, Van Dam FS. Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *Journal of Clinical Oncology.* 2004;22:2233-2239.
(9) Bender CM, Pacella ML, Sereika SM et al. What do perceived cognitive problems reflect? *J Support Oncol.* 2008;6:238-242.
(10) Schagen SB, Van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer.* 1999;85:640-650.
(11) 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.
(12) Middleton LS, Denney DR, Lynch SG, Parmenter B. The relationship between perceived and objective cognitive functioning in multiple sclerosis. *Arch Clin Neuropsychol.* 2006;21:487-494.
(13) Lannoo E, Colardyn F, Vandekerckhove T, De Deyne C, De Soete G, Jannes C. Subjective complaints versus neuropsychological test performance after moderate to severe head injury. *Acta Neurochir (Wien).* 1998;140:245-253.
(14) Velissaris SL, Wilson SJ, Newton MR, Berkovic SF, Saling MM. Cognitive complaints after a first seizure in adulthood: Influence of psychological adjustment. *Epilepsia.* 2009;50:1012-1021.
(15) Bedi G, Redman J. Metamemory in recreational ecstasy polydrug users: what do self-reports of memory failures mean? *J Psychopharmacol.* 2008;22:872-881.
(16) Weaver Cargin J, Collie A, Masters C, Maruff P. The nature of cognitive complaints in healthy older adults with and without objective memory decline. *J Clin Exp Neuropsychol.* 2008;30:245-257.
(17) Reid LM, Maclullich AM. Subjective memory complaints and cognitive impairment in older people. *Dement Geriatr Cogn Disord.* 2006;22:471-485.
(18) Vestberg S, Passant U, Elfgren C. Stability in the clinical characteristics of patients with memory complaints. *Arch Gerontol Geriatr.* 2010;50:e26-e30.

(19) Lai JS, Butt Z, Wagner L et al. Evaluating the dimensionality of perceived cognitive function. *J Pain Symptom Manage.* 2009;37:982-995.
(20) Pearman A, Storandt M. Self-discipline and self-consciousness predict subjective memory in older adults. *J Gerontol B Psychol Sci Soc Sci.* 2005;60:153-157.
(21) Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Ann Oncol.* 2002;13:589-598.
(22) McDonald-Miszczak L, Hertzog C, Hultsch DF. Stability and accuracy of metamemory in adulthood and aging: a longitudinal analysis. *Psychol Aging.* 1995;10:553-564.
(23) Christodoulou C, Melville P, Scherl WF et al. Perceived cognitive dysfunction and observed neuropsychological performance: longitudinal relation in persons with multiple sclerosis. *J Int Neuropsychol Soc.* 2005;11:614-619.
(24) Lezak M. *Neuropsychological assessment*. New York: Oxford University Press; 2004.
(25) van Nes JG, Seynaeve C, Maartense E et al. Patterns of care in Dutch postmenopausal patients with hormone-sensitive early breast cancer participating in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. *Ann Oncol.* 2009; Oct 29, e-pub ahead of print.
(26) Schilder CM, Seynaeve C, Beex LV et al. Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial. *J Clin Oncol.* 2010;28:1294-1300.
(27) 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.
(28) 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.
(29) Schilder CM, Eggens PC, Seynaeve C et al. Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: Cross-sectional findings from the neuropsychological TEAM-side study. *Acta Oncol.* 2009;48:76-85.
(30) Van der Meulen EF, Schmand B, van Campen JP et al. The seven minute screen: a neurocognitive screening test highly sensitive to various types of dementia. *Journal of Neurology Neurosurgery & Psychiatry.* 2004;75:700-705.
(31) Huyser Y. *De symptomatologie van depressieve stoornissen en angststoornissen.* Amsterdam: Benecke Consultants; 2004.
(32) Van Dam FS, Schagen SB, Muller MJ et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst.* 1998;90:210-218.
(33) Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol.* 1982;21 (Pt 1):1-16.
(34) Ponds RW, Roozendaal N, Jolles J. *The cognitive failure questionnaire: factor structure, effects of age, sex and education and the relation with cognitive performance and psychosocial variables.* Maastricht: University of Maastricht, 2004.
(35) Frojdh K, Hakansson A, Karlsson I. The Hopkins Symptom Checklist-25 is a sensitive case-finder of clinically important depressive states in elderly people in primary care. *Int J Geriatr Psychiatry.* 2004;19:386-390.
(36) Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365-376.

(37) Fallowfield LJ, Leaity SK, Howell A, Benson S, Cella D. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. *Breast Cancer Res Treat.* 1999;55:189-199.
(38) Wechsler D. *Wechsler Memory Scale: Revised*. New York: Psychological Corporation; 1987.
(39) Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills.* 1958;8:271-276.
(40) Hammes J. *De Stroop kleur-woord test. Handleiding*. second ed. Lisse: Swets & Zeitlinger; 1978.
(41) Wechsler D. *WAIS-III Nederlandstalige Bewerking. Technische Handleiding.* Lisse: Swets & Zeitlinger; 2000.
(42) Alpherts W, Aldenkamp AP. *FePsy: the iron psyche*. Heemstede: Instituut voor Epilepsiebestrijding; 1994.
(43) Van der Elst W, van Boxtel MP, Van Breukelen GJ, Jolles J. Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *Journal of the International Neuropsychological Society.* 2006;12:80-89.
(44) Schmand B, Groenink SC, van den Dungen M. [Letter fluency: psychometric properties and Dutch normative data] Letterfluency: psychometrische eigenschappen en Nederlandse normen. *Tijdschr Gerontol Geriatr.* 2008;39:64-76.
(45) Schmand B, Lindeboom J, van Harskamp F. *De Nederlandse Leestest voor Volwassenen*. Lisse: Swets & Zeitlinger; 1992.
(46) Pfeifer S, van Os J, Hanssen M, Delespaul P, Krabbendam L. Subjective experience of cognitive failures as possible risk factor for negative symptoms of psychosis in the general population. *Schizophr Bull.* 2009;35:766-774.
(47) Jenkins VA, Ambroisine 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.
(48) Cull A, Hay C, Love SB, Mackie M, Smets E, Stewart M. What do cancer patients mean when they complain of concentration and memory problems? *Br J Cancer.* 1996;74:1674-1679.
(49) 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.
(50) Schagen SB, Vardy J. Cognitive dysfunction in people with cancer. *Lancet Oncol.* 2007;8:852-853.