original reports

Brain White Matter Microstructure as a Risk Factor for Cognitive Decline After Chemotherapy for Breast Cancer

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abstract

PURPOSE Cognitive decline is frequently observed after chemotherapy. As chemotherapy is associated with changes in brain white matter microstructure, we investigated whether white matter microstructure before chemotherapy is a risk factor for cognitive decline after chemotherapy.

METHODS Neuropsychologic tests were administered before and 6 months (n = 49), 2 years (n = 32), and 3 years (n = 32) after chemotherapy in patients with breast cancer receiving anthracycline-based chemotherapy (BC + CT group), at matched intervals to patients with BC who did not receive systemic therapy (BC – CT group: n = 39, 23, and 19, respectively) and to no-cancer controls (NC group: n = 37, 29, and 28, respectively). Using multivariate normative comparison, we evaluated to what extent the cognitive profiles of patients deviated from those of controls. Fractional anisotropy (FA), derived from magnetic resonance diffusion tensor imaging, was used to measure white matter microstructure before treatment. FA was evaluated as a risk factor for cognitive decline, in addition to baseline age, fatigue, cognitive complaints, and premorbid intelligence quotient. We subsequently ran voxel-wise diffusion tensor imaging analyses to investigate white matter microstructure in specific nerve tracts.

RESULTS Low FA independently predicted cognitive decline early (6 months, $P = .013$) and late (3 years, $P < .001$) after chemotherapy. FA did not predict cognitive decline in the BC – CT and NC groups. Voxel-wise analysis indicated involvement of white matter tracts essential for cognitive functioning.

CONCLUSION Low FA may reflect low white matter reserve. This may be a risk factor for cognitive decline after chemotherapy for BC. If validated in future trials, identification of patients with low white matter reserve could improve patient care, for example, by facilitating targeted, early interventions or even by influencing choices of patients and doctors for receiving chemotherapy.

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INTRODUCTION

Cognitive decline after chemotherapy has been demonstrated reliably and repeatedly in 20%-40% of patients with cancer.[1,2] It may last well into the survivorship period and interferes with daily living skills and quality of life.[3,4] Identification of patients with cancer who are at risk for cognitive decline after chemotherapy could improve patient care, for example, by facilitating targeted, early interventions.[4,5]

Many clinical and preclinical studies point to neurotoxic properties of various chemotherapeutic agents[2,6] including anthracycline-based regimens.[7] Therefore, patients who are vulnerable to neurotoxicity from chemotherapy may be at increased risk of cognitive decline. Various patient-related risk factors for cognitive decline after chemotherapy have been reported, including genetic makeup,[4] high age,[8-10] fatigue,[11] low educational level,[6] and low premorbid intelligence quotient (IQ).[8,12] An understudied risk factor for cognitive decline after chemotherapy is a low brain reserve.[13] Brain reserve refers to individual variation in structural characteristics of the brain (eg, white matter microstructure and cortical thickness). These variations in brain reserve may explain why some individuals are more vulnerable to adverse effects on the brain than others. In populations outside oncology, several studies used magnetic resonance diffusion tensor imaging (DTI) studies to derive fractional anisotropy (FA) as a measure for brain reserve. FA is related to the directionality of water diffusion along axonal fibers. Physical properties of fiber bundles, such as myelination and axon density, are known to influence FA.[14] A low FA is generally suggestive of impaired white matter microstructure. For instance, low FA in the genu of the corpus callosum has been found to predict general cognitive decline[15] and decline in visuospatial memory later in late middle age,[16]

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Is magnetic resonance imaging–based brain white matter microstructure before chemotherapy for breast cancer a risk factor for cognitive decline after chemotherapy?

Knowledge Generated

A low fractional anisotropy, reflecting white matter microstructure, predicted cognitive decline 6 months and 3 years after chemotherapy, independent of age, premorbid intelligence quotient, baseline fatigue, and baseline cognitive complaints.

Relevance

Low fractional anisotropy may reflect low white matter reserve, putting a patient at risk for chemotherapy-associated cognitive decline. If validated in future trials, identification of patients with low white matter reserve could improve patient care, for example, by facilitating targeted, early interventions or even by influencing choices of patients and doctors for receiving chemotherapy.

low global FA has been found to predict later mild cognitive impairment,[17] and network measures based on FA have been found to predict general cognitive decline, memory, and executive function in cerebral small vessel disease.[18]

Many studies in the field of cancer and cognition, including work from our own group, show that exposure to chemotherapy is associated with changes in brain white matter microstructure—predominantly decreases in FA—and is sometimes directly associated with cognitive decline.[19-30] This makes FA an obvious candidate to study brain reserve and cognitive decline after chemotherapy.

Here, we investigated whether patients with breast cancer (BC) before treatment are vulnerable to cognitive decline after receiving anthracycline-based chemotherapy, sometimes followed by endocrine therapy. To this end, we evaluated cognitive decline at three follow-up (FU) assessments: approximately 6 months, 2 years, and 3 years after chemotherapy. We compared patients with BC who received chemotherapy (BC + CT group) with two control groups: patients with BC who did not receive systemic cancer therapy (BC – CT group) and women with no cancer diagnosis (NC group). To evaluate the specificity of low FA as a risk factor for cognitive decline after chemotherapy, we also evaluated previously identified risk factors: older age,[8-10] low premorbid IQ,[8,12] high fatigue levels, and cognitive complaints before the start of treatment.[11] We hypothesized (1) that a low FA before chemotherapy predicts cognitive decline early (6 months) and late (≥ 2 years) after chemotherapy and (2) that white matter tracts essential for cognitive function would be involved.

METHODS

Study Sample and Research Design

Participants were recruited as part of a study funded by the Dutch Cancer Society. The study was approved by the Institutional Review Board of the Netherlands Cancer Institute, serving as the central ethical committee for all participating institutes. The present study comprises four time points and was an extension of a previous study for which additional participants were recruited and two time points (2 and 3 years post-treatment) were added.[12,27,30-32] The study was conducted at two scan locations. Written informed consent was acquired on the basis of the Declaration of Helsinki and institutional guidelines. Patients were recruited at four hospitals: the Netherlands Cancer Institute, Amsterdam University Medical Centers, Flevoziekenhuis, and Reinier de Graaf Gasthuis.

Patients in the BC + CT group were scheduled to receive adjuvant anthracycline-based chemotherapy with or without endocrine therapy. Patients in the BC – CT group did not receive systemic therapy. Participants were eligible when they met the following criteria: female, younger than 70 years, sufficient command of the Dutch language, no previous malignancies, and no history of neurologic or psychiatric conditions. Additionally, patients had to have a diagnosis of primary BC, no distant metastases, and no other treatment than surgery at the time of baseline assessment. Participants in the NC group were recruited via patients, as well as through advertisements in the participating hospitals. For patients, baseline data were collected after surgery and before receiving adjuvant chemotherapy. Three FU sessions took place on average 6 months, 2 years, and 3 years after chemotherapy for the BC + CT group and at matched intervals for BC – CT and NC groups.

Study Measures

The assessment included a neuropsychologic test battery, patient-reported outcomes measures, including assessment of self-reported fatigue and cognitive functioning with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30,[33] and multimodality magnetic resonance imaging (MRI).[12] These measures are detailed in the Data Supplement (online only). Premorbid IQ was assessed with the Dutch Adult Reading Test.[34] The MRI protocol included a DTI scan

(32 directions, b value: 1,000 s/mm^2) and a T1-weighted magnetization-prepared rapid gradient-echo scan for registration purposes. Here, the DTI and T1 scans acquired at baseline were used.

Definition of Cognitive Decline

Cognitive decline was evaluated with a method that takes into account the correlations between tests and determines whether a profile of scores is deviant from expected profiles: per FU assessment, we calculated a continuous outcome measure reflecting cognitive decline for each individual using multivariate normative comparison.[12,35-37] We additionally calculated a binary outcome measure (impaired or not impaired) to verify whether BC + CT patients were more often cognitively impaired than BC – CT patients and NC participants at each FU assessment. This approach is explained in more detail in the Data Supplement.

Computation of FA

We used DTI-derived FA at baseline (ie, before chemotherapy) as a measure for white matter microstructure. We used a DTI processing pipeline as described in Mzayek et al.[30] This processing pipeline allows using more voxels for statistical analysis compared with tract-based spatial statistics[38] (Data Supplement).

Statistical Analysis

For comparison of baseline demographics, clinical characteristics, and cognitive outcomes (ie, the primary continuous measure of cognitive decline and the additional binary measure of cognitive impairment), we used analyses of variance (ANOVAs) for continuous variables and $\chi 2$ test for categorical variables.

DTI as Predictor of Cognitive Decline

Multiple regression analyses. We performed stepwise backward multiple regression analyses using cognitive decline at each FU as outcome measure. We first ran three moderated multiple regression analyses (one analysis for each FU) including Group as a moderator, FA, baseline age, self-reported cognitive functioning, fatigue, IQ, and interactions with Group. We also modeled scan location and the interaction with FA. When the multiple regression model was significant at the level of 0.01, we considered the interactions of Group with other predictors (significance level 0.05). When we found a significant Group × predictor interaction at a FU measurement, we ran a separate multiple regression analysis for that group. Again, only when the multiple regression model was significant at the level of 0.01, we considered the individual variables within that model.

All multiple regression analyses were performed with SPSS version 26.0 (IBM, Armonk, NY).

Effect sizes were calculated as appropriate for the statistical test. Numbers between parentheses represent thresholds for small, medium, and large effect sizes, respectively: Cohen's *d* for ANOVA (0.2, 0.5, and 0.8), φ for $\chi 2$ test (0.1, 0.3, and 0.5), and f^2 for regression analysis (0.02, 0.15, and 0.35). We could not distinguish between BC + CT patients with or without endocrine therapy as the majority (67%) of BC + CT patients received endocrine therapy.

Voxel-wise analyses. To reveal white matter tracts predictive of cognitive decline, a nonparametric general linear model using *randomise*[39] in FMRIB Software Library[40] was applied, testing the association between baseline voxel-wise FA and cognitive decline. We first ran models per FU assessment including the factor Group and then for each group that showed a significant interaction of Group and baseline FA. The parameters for *randomise* included 5,000 permutations and threshold-free cluster enhancement to correct for multiple comparisons.[41] Scan location was included as a covariate. For the voxel-wise analyses, we did not include other predictors besides FA to retain maximal sensitivity to detect specific white matter regions predictive for cognitive decline. Outcomes were considered statistically significant at a family-wise error–corrected α of .05.

RESULTS

Study Sample

The flowchart (Fig 1) shows participant attrition for the consecutive assessments. There was a considerable rate of discontinuation from FU1 (6 months postchemotherapy) to FU2 and 3 (2 and 3 years postchemotherapy), probably because the latter time points were a study extension that was not known to participants beforehand and took place relatively long after FU1. In addition, some patients were not approached for the extension study because they fell outside the inclusion window. Baseline DTI was not acquired in all participants, particularly patients. This reflects apprehensiveness of patients to undergo MRI, time constraints of patients scheduled for chemotherapy, scanner failure, and scanner unavailability. For three NC participants, DTI was acquired in the sagittal instead of transversal direction. As FA values were considerably higher in these participants, these values were removed from analyses (Data Supplement).

Mean baseline FA and baseline cognitive functioning (adjusted Hotelling's T^2) were not significantly associated for any of the three groups (all *P*s $>$ .43).

There was an overrepresentation of participants who were cognitively impaired at FU1 who continued participation in the BC + CT group (41% *v* 31% in total sample at FU1) and in the NC group (10% *v* 8% in total sample at FU1). There was an underrepresentation of cognitively impaired patients at FU1 who continued participation in the BC – CT group (10% *v* 18% in total sample at FU1). BC + CT patients who continued participation had a somewhat lower FA at baseline (0.325 ± 0.010) than BC + CT patients who did not continue participation (0.330 ± 0.010). This was, however, not significantly different as evaluated with analysis of covariance ($F(1,34) = 2.385$, $P = .132$).

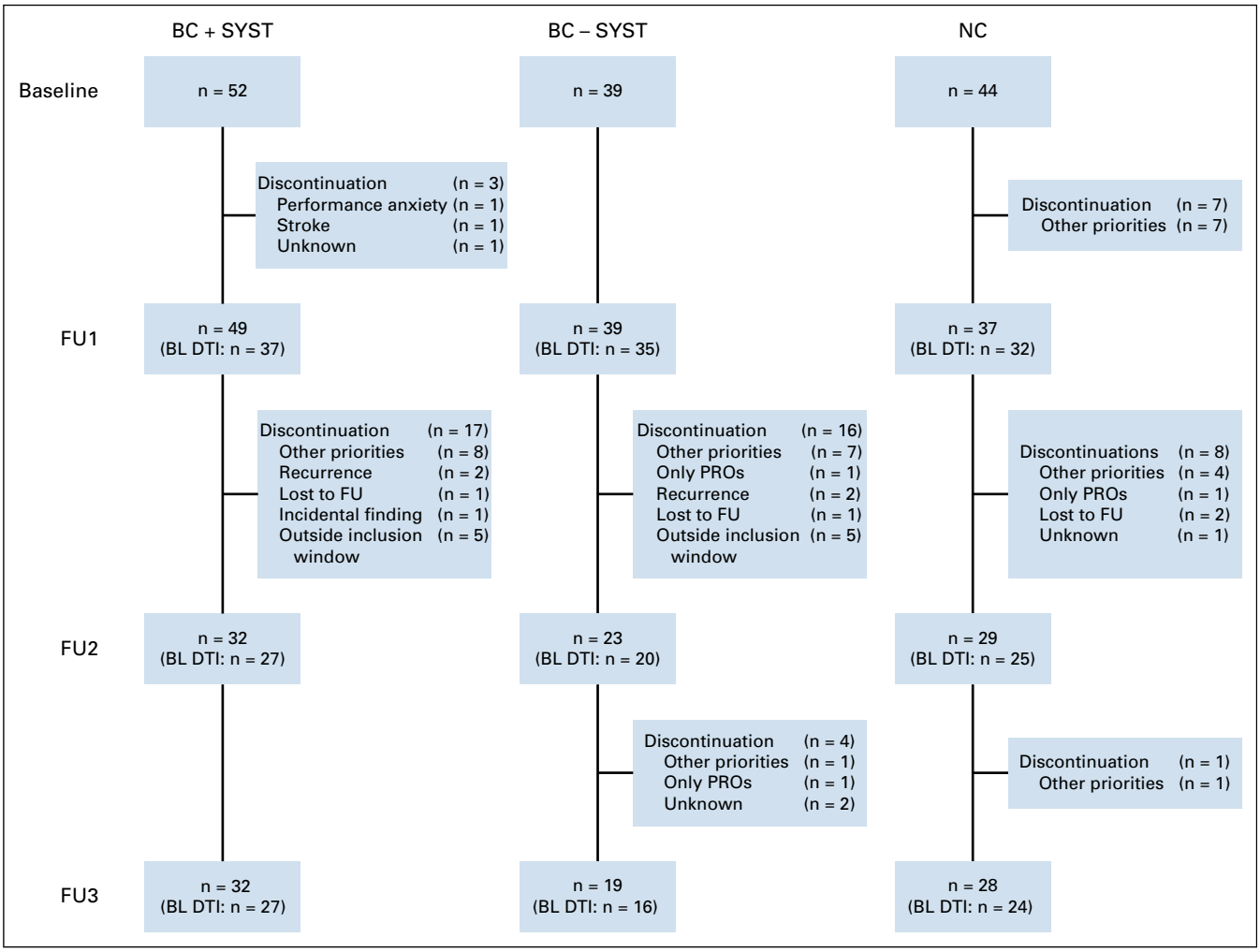

FIG 1. Flowchart. BC, breast cancer; BC + SYST, patients with BC who received systemic therapy; BC – SYST, patients with BC who did not receive systemic therapy; FU, follow-up; BL DTI, baseline diffusion tensor imaging; NC, no control; PROs, patient-reported outcomes.

Baseline Characteristics

For 49 BC + CT patients, 39 BC – CT patients, and 37 NC participants, neuropsychologic data were available at baseline and FU1 (Table 1). All BC + CT patients received anthracycline-based chemotherapy, and 67% of them received endocrine therapy. No significant group differences in age and educational level were found. Compared with controls, patients reported higher levels of fatigue and distress and lower levels of cognitive functioning and global quality of life. Premorbid IQ and FA did not differ significantly between groups (Table 1). Baseline characteristics for the participants for whom baseline FA data and cognitive data at FU3 were available were similar to the characteristics of the complete sample (Data Supplement).

Cognitive Decline

For the continuous outcome measure of cognitive decline, no significant group differences were apparent from baseline to FU1 and 2 (on average 7.1 and 27.4 months after chemotherapy). For FU3 (on average 40.4 months after chemotherapy), performance was worse for the BC + CT group than the BC – CT group. This effect was, however, not statistically significant (post hoc test $P = .022$, ES [Cohen's d] = 0.717; Table 2).

With regard to the binary outcome measure for cognitive impairment, at FU1, 31% of the BC + CT patients showed significant cognitive impairment compared with baseline, compared with 18% of the BC – CT group and 8% of the NC group. This difference was statistically significant ($P = .033$). Post hoc tests indicated that the BC + CT group differed significantly from the NC group ($P = .011$, ES(φ) = .274) but not from the BC – CT group ($P = .173$). The differences between the BC + CT and BC – CT group were also not statistically significant ($P = .205$). At FU2 and 3, no statistically significant differences in the percentage of participants showing cognitive impairment were found, although the percentage of patients with cognitive impairment was numerically higher in the BC + CT group compared with the other groups (Table 2).

TABLE 1. Baseline Characteristics and FU Assessments

Variable	BC + CT (n = 49)	BC − CT (n = 39)	NC (n = 37)	*P*
Age, years	50.0 (9.4)	49.8 (7.5)	49.9 (10.3)	.995
Education, frequency, No. (%)				
Low	4 (8)	5 (13)	0 (0)	.187
Intermediate	33 (67)	27 (69)	31 (84)	
High	12 (25)	7 (18)	6 (16)	
Breast cancer stage, frequency, No. (%)				
0	0 (0)	20 (51)	—	
I	29 (59)	19 (49)	—	
II	19 (39)		—	
III	1 (2)		—	
Treatment, frequency, No. (%)				
Chemotherapy	49 (100)	0 (0)	—	
Endocrine therapy	33 (67)	0 (0)	—	
Radiotherapy	35 (71)	20 (51)	—	
Scanner location, frequency, No. (%)	13/24 (35/65)	12/23 (34/66)	16/16 (50/50)	.338
EORTC QLQ-C30				
Fatigue[a]	29.3 (25.2)	35.3 (23.8)	15.0 (18.7)	< .001[b,c]
Physical functioning[d]	88.4 (14.5)	86.5 (14.4)	95.9 (9.3)	.006[c]
Social functioning[d]	76.9 (26.5)	75.2 (24.4)	99.1 (5.4)	< .001[b,c]
Cognitive functioning[d]	77.6 (25.1)	77.4 (25.8)	91.9 (14.0)	.006[b,c]
Global quality of life[d]	74.0 (17.1)	72.4 (15.5)	87.6 (10.5)	< .001[b,c]
HSCL-25[a]	12.7 (10.7)	12.6 (11.0)	5.7 (5.7)	.002[b,c]
PSS[a]	24.6 (6.2)	21.2 (7.6)	18.7 (4.8)	< .001[b]
POMS				
Total score[a]	15.2 (11.7)	14.9 (10.4)	8.4 (4.1)	.004[b,c]
Fatigue[a]	2.5 (3.5)	3.4 (4.8)	1.1 (1.4)	.027[c]
MOS-Cog[d]	73.2 (18.4)	65.7 (20.2)	82.2 (13.7)	< .001[c]
Premorbid IQ	101.7 (13.7)	104.0 (12.6)	106.6 (13.0)	.238
FA	.33 (.01)	.33 (.01)	.33 (.01)	.873
Time since baseline assessment, months				
FU1	11.5 (3.0)	11.4 (1.5)	12.1 (2.1)	.400
FU2	31.6 (3.1)	31.9 (3.3)	32.8 (2.1)	.267
FU3	44.5 (4.0)	47.1 (3.8)	45.8 (3.0)	.236
Time since chemotherapy, months				
FU1	7.1 (2.8)			
FU2	27.5 (3.6)			
FU3	40.5 (4.2)			

NOTE. Baseline characteristics are shown for participants for whom neuropsychologic data were available at baseline and FU1. Characteristics of the full baseline sample were similar. Means are shown with SD in parentheses and frequencies are shown with percentages in parentheses. *P* values indicate overall group differences. Bold indicates variables used in regression analyses. Scanner location indicates where magnetic resonance imaging scans were acquired (Spinoza Centre/Amsterdam University Medical Centers, location AMC). For scanner location and baseline FA—BC + CT: n = 37, BC – CT: n = 35, and NC: n = 32. For additional sample sizes, see Figure 1 and the Data Supplement. When radiotherapy was part of the treatment, this typically commenced after the baseline assessment. FU1 always took place after completion of radiotherapy.

Abbreviations: BC, breast cancer; BC + CT, patients with BC who received adjuvant chemotherapy with or without endocrine treatment; BC – CT, patients with BC who did not receive systemic treatment; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer health-related Quality of life Questionnaire: scores range from 0 to 100; FA, fractional anisotropy; FU, follow-up; HSCL-25, Hopkins Symptom Checklist-25: scores range from 0 to 100; MOS-cog, Cognitive Functioning Scale—revised of the Medical Outcomes Study; NC group, women with no cancer diagnosis; POMS, Profile of Mood States; PSS, Perceived Stress Scale: scores range from 10 to 50; SD, standard deviation.

[a]Higher score indicates more symptoms.

[b]Post hoc tests showing a significant difference between BC + CT and NC, indicating more symptoms or worse functioning for patients than controls, at $P < .01$.

[c]Post hoc tests showing a significant difference between BC – CT and NC, indicating more symptoms or worse functioning for patients than controls, at $P < .01$.

[d]Higher score indicates better functioning.

There were no tests indicating that patients had less symptoms or better functioning than controls.

TABLE 2. FU Assessments

FU1	BC + CT (n = 49)	BC – CT (n = 39)	NC (n = 37)	*P*
Cognitive decline, continuous	–0.45 (2.95)	0.01 (2.22)	–0.15 (1.55)	.652
Cognitive impairment, binary: No. (%)	15 (31)	7 (18)	3 (8)	.033a
FU2	**BC + CT (n = 32)**	**BC – CT (n = 23)**	**NC (n = 29)**	***P***
Cognitive decline, continuous	–0.85 (2.55)	0.14 (2.25)	–0.59 (1.48)	.233
Cognitive impairment, binary: No. (%)	8 (25)	4 (17)	4 (14)	.523
FU3	**BC + CT (n = 32)**	**BC – CT (n = 19)**	**NC (n = 28)**	***P***
Cognitive decline, continuous	–0.92 (2.00)	0.29 (1.30)	–0.50 (1.81)	.070b
Cognitive impairment, binary: No. (%)	6 (19)	0 (0)	5 (18)	.132

NOTE. Cognitive decline and cognitive impairment are measured with multivariate normative comparison, adjusted Hotelling's T^2 (see text for details). Means are shown with SD in parentheses and frequencies are shown with percentages in parentheses.

Abbreviations: BC, breast cancer; BC + CT, patients with BC who received adjuvant chemotherapy with or without endocrine therapy; BC – CT, patients with BC who did not receive systemic therapy; FU, follow-up; NC group, women with no cancer diagnosis; SD, standard deviation.

[a]BC + CT versus NC: $P = .011$, ES (φ) = .274; BC + CT versus BC – CT: $P = .173$; BC – CT versus NC: $P = .205$.

[b]BC + CT versus NC: $P = .362$; BC + CT versus BC – CT: $P = .022$, ES (Cohen's d) = .717; BC – CT versus NC: $P = .141$.

TABLE 3. Multiple Regression Analyses

Assessment	Variable	*B*	SE *B*	B	*t*	*P*	f^2	R^2	*P*
FU1									
Including groups								.191	< .001
	BC + CT × FA	1.144	.386	.266	2.962	.004	.088		
	BC + CT × IQ	.980	.320	.276	3.064	.003	.094		
BC + CT								.301	.002
	IQ	.075	.027	.394	2.746	.010	.222		
	FA	98.304	37.604	.375	2.614	.013	.200		
FU2									
Including groups								.355	< .001
	BC + CT × IQ	1.180	.338	.347	3.487	< .001	.181		
	BC – CT × IQ	1.673	.447	.370	3.742	< .001	.209		
	BC – CT × fatigue	1.136	.447	.328	2.541	.013	.096		
BC + CT								.329	.008
BC – CT								.388	.003
	IQ	.112	.033	.623	3.378	.003	.634		
FU3									
Including groups								.224	.007
	BC + CT × FA	1.440	.553	.357	2.607	.011	.112		
	BC – CT × fatigue	1.273	.583	.335	2.184	.033	.079		
BC + CT								.445	.003
	FA	207.621	53.398	1.083	3.888	< .001	.658		

Abbreviations: BC, breast cancer; BC + CT, patients with BC who received adjuvant chemotherapy with or without endocrine therapy; BC – CT, patients with BC who did not receive systemic therapy; NC group, women with no cancer diagnosis; Cognitive decline as measured with the adjusted Hotelling's T^2 was used as the dependent variable. f^2, effect size (≥ 0.02, ≥ 0.15, and ≥ 0.35 represent small, medium, and large effect sizes, respectively); FA; fractional anisotropy; FU, follow-up.

Baseline Predictors of Cognitive Decline at FU1, 2, and 3

Multiple regression analyses. At FU1, significant BC + CT × FA and BC + CT × IQ interactions indicated that the effects of baseline FA and IQ were different for the BC + CT group than the other two groups. This was confirmed by the regression analysis in the BC + CT group that showed significant effects of medium size for both variables, indicating lower baseline levels of FA and IQ predicted cognitive decline. At FU2, significant BC + CT × IQ, BC – CT × IQ, and BC – CT × Fatigue interactions were confirmed by significant effects of IQ in the separate analyses for the BC – CT group, indicating lower IQ predicted cognitive decline (large effect size). At FU3, significant BC + CT × FA and BC – CT × Fatigue interactions were only confirmed by a significant regression analysis for the BC + CT group, showing that low baseline FA predicted cognitive decline (large effect size; Table 3).

Voxel-wise DTI analyses. Similar to the multiple regression analyses, the voxel-wise DTI analyses showed that low baseline FA predicted cognitive decline in the BC + CT group for FU1 and 3 (analyses involving Group followed by per-group analyses). The BC + CT > BC – CT contrast showed that clusters overlapping with a number of white matter tracts predicted cognitive decline at FU 1 and/or 3 in the BC + CT group but not the BC – CT group: cerebral peduncle; inferior fronto-occipital fasciculus; thalamic radiation; and the middle and superior longitudinal fasciculi. In addition, the BC + CT > NC contrast showed clusters including cerebral peduncle; inferior fronto-occipital fasciculus; thalamic radiation; and the inferior, middle, and superior longitudinal fasciculi at FU3. Per-group analyses showed clusters overlapping with a number of white matter tracts predicted cognitive decline at FU 1 and/or 3 in the BC + CT group: cerebral peduncle; inferior fronto-occipital fasciculus; thalamic radiation; and the inferior, middle, and superior longitudinal fasciculi (Fig 2). For the other groups, low baseline FA did not predict cognitive decline at any FU assessment. Scatter plots show the association of baseline FA and cognitive decline in the BC + CT group (Fig 3).

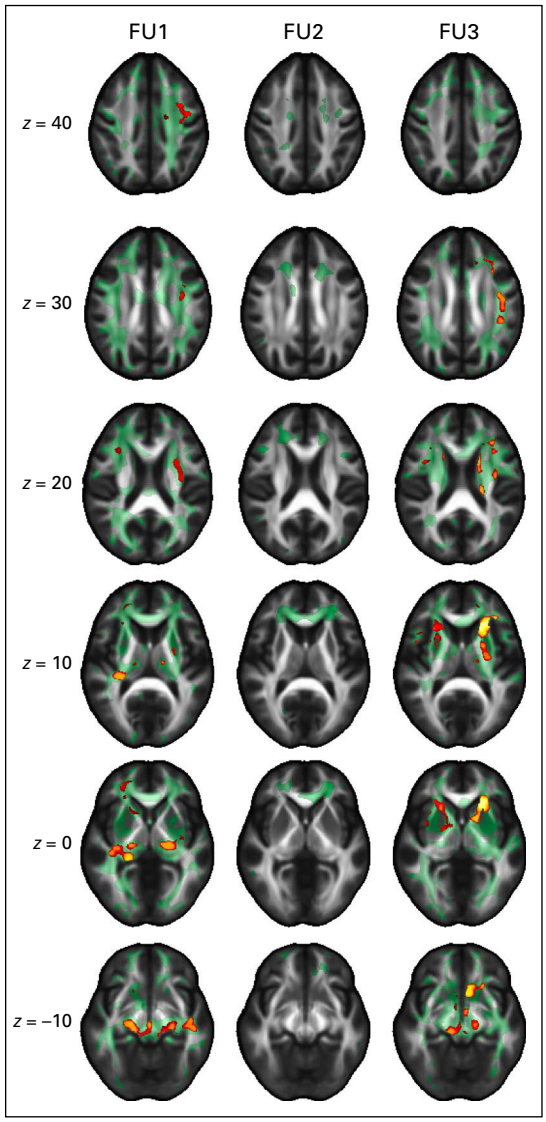

FIG 2. Baseline diffusion tensor imaging–derived fractional anisotropy as a predictor of cognitive decline after chemotherapy in the BC + CT group at the three FU assessments (6 months, 2 years, and 3 years after chemotherapy). Significant clusters are shown family-wise error–corrected at $P < .05$ in red/yellow and include cerebral peduncle; inferior fronto-occipital fasciculus; thalamic radiation; and the inferior, middle, and superior longitudinal fasciculi. To show the extent of the effects, uncorrected P values $< .05$ are shown in green. z values refer to the Montreal Neurological Institute template. BC + CT, patients with breast cancer who received chemotherapy; FU, follow-up.

DISCUSSION

We observed that low FA before chemotherapy is a risk factor for early and late cognitive decline after chemotherapy for BC. Low FA in nerve tracts pivotal for cognitive function predicted cognitive decline both early (6 months) and late (3 years) following chemotherapy. In addition, low premorbid IQ was an independent risk factor for cognitive decline after chemotherapy, in line with previous findings.[8,12] Some women in the BC – CT and NC group also showed cognitive decline, albeit to a lesser extent. Crucially, FA did not predict cognitive decline in these groups, indicating that a low FA is a specific risk factor for cognitive decline after chemotherapy.

Voxel-wise analyses showed involvement of white matter regions and tracts, including those that are critically involved in several (often overlapping) cognitive functions,[42] such as the inferior, middle, and superior longitudinal fasciculi (visual cognition, language, attention, and memory)[23,42-45]; inferior fronto-occipital fasciculus (visual processing and memory)[42,43,46]; cerebral peduncle (dexterity)[47,48]; and thalamic radiations (attention).[49]

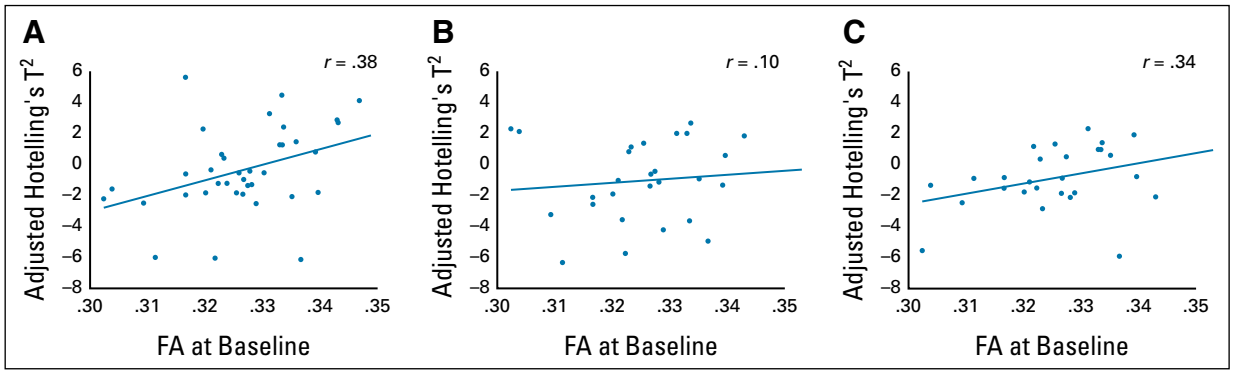

FIG 3. Scatter plots depicting associations between FA at baseline and cognitive decline at the three FU assessments (approximately 6 months, 2 years, and 3 years after chemotherapy): (A) FU1, (B) FU2, and (C) FU3. *x*-axis shows mean FA values across whole-brain white matter. *y*-axis shows adjusted Hotelling's T^2. *P* values for Pearson correlations are .019, .61, and .080, respectively (see main text for details). FA, fractional anisotropy; FU, follow-up.

We found that FA had a medium effect size for predicting cognitive decline at 6 months postchemotherapy, whereas the effect size was large for predicting cognitive decline at 3 years postchemotherapy. This might indicate that a low white matter reserve is a particularly strong risk factor for late cognitive decline. However, as there was considerable patient attrition at the 3-year FU, this finding should be interpreted with caution.

Interestingly, baseline FA was not a risk factor for cognitive decline 2 years after chemotherapy. Low statistical power cannot explain this finding as the number of BC + CT patients was identical for the 2- and 3-year FU. Visual inspection of the data revealed that two patients showed temporary recovery from cognitive decline at 2 years, compared with the 6-month and 3-year FU. Perhaps these patients were temporarily able to compensate for low white matter integrity, obscuring the association between white matter reserve and cognitive decline at 2 years.[50]

To our knowledge, this is the first study presenting evidence for structural neuroimaging measures acquired pretreatment being predictive for cognitive decline after chemotherapy for BC. The finding that a low baseline FA is a risk factor for cognitive decline after chemotherapy in patients with BC has potential clinical implications. A low FA might represent a low brain white matter reserve. When confirmed in future studies, such information could assist in weighing the risks and benefits of treatment strategies,[51] where clinically validated assessments of white matter reserve as assessed with an MRI scan may be part of a pretreatment screening. This could also aid in early identification of cognitive decline after chemotherapy, allowing targeted and early interventions to improve cognitive problems (eg, psychoeducation and cognitive rehabilitation).[4,5]

Several limitations should be noted for the present study. Although low baseline FA exclusively predicted cognitive decline after treatment with chemotherapy, group differences in cognitive decline at the FUs were minimal. We were not able to acquire baseline DTI in a considerable number of participants, particularly patients. There was also substantial patient attrition, most notably between FU1 and FU2, potentially because of the fact that FU2 and FU3 were an extension of a previous study. Patients were therefore not informed about the extension beforehand. We had to approach women again to invite them to the new study where sometimes they would rather not be reminded of that burdensome period in their lives. Chemotherapy-exposed patients who showed cognitive decline at 6 months were more likely to participate in the 2- and 3-year FUs than those who did not show cognitive decline at 6 months. Although this may have led to an overestimation of late cognitive decline, this does not necessarily mean that it biased the associations between baseline FA and late cognitive decline. About two thirds of patients who completed chemotherapy at the three FU assessments were prescribed and typically still receiving endocrine therapy. Because of low statistical power, we did not evaluate whether the predictive effect of baseline FA on cognitive decline differed for patients with or without endocrine therapy. More advanced diffusion-weighted imaging techniques and analytical approaches address some of the limitations of DTI (eg, improved interpretation of microstructural changes at crossing fibers) and might be preferred when further investigating the role of white matter reserve in cognitive decline after chemotherapy.[52] Participants were only eligible for participation when they were younger than 70 years because at the time of inclusion, chemotherapy was only indicated for patients with BC up to age 70 years. Future studies should also include older participants as this group may be particularly vulnerable to the effects of chemotherapy on cognitive functioning.[53] Finally, we may not have included all variables that could explain associations of baseline FA with cognitive decline.

Strong aspects of this study are the longitudinal design, the use of brain MRI to measure risk factors for chemotherapy-associated cognitive decline, the use of an advanced

analytic approach to capture cognitive decline in a single outcome measure, the inclusion of three FU assessments up to 3 years postchemotherapy, and the inclusion of two control groups to assess the exclusive involvement of FA as a risk factor for cognitive decline following chemotherapy.

In conclusion, our findings indicate that low white matter reserve is a risk factor for cognitive decline after chemotherapy for BC. When confirmed in future studies, MRI-based assessments of white matter reserve might be part of a pretreatment screening to weigh risks and benefits of chemotherapy in the individual patient.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Brain White Matter Microstructure as a Risk Factor for Cognitive Decline After Chemotherapy for Breast Cancer

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