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Long-term cognitive function change among breast cancer survivors

Ying Zheng,
Department of Cancer Prevention and Control, Shanghai Municipal Center for Disease Control and Prevention, Shanghai 200336, China

Jianfeng Luo,
Department of Health Statistics and Social Medicine, School of Public Health, Fudan University, Shanghai 200032, China

Pingping Bao,
Department of Cancer Prevention and Control, Shanghai Municipal Center for Disease Control and Prevention, Shanghai 200336, China

Hui Cai,
Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, 2525 West End Ave, Suite 300, Nashville, TN 37203-1738, USA

Zhen Hong,
Department of Neurology, Shanghai Hua Shan Hospital, Fudan University, Shanghai 200051, China

Ding Ding,
Department of Neurology, Shanghai Hua Shan Hospital, Fudan University, Shanghai 200051, China

James C. Jackson,
Division of Critical Care, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN 37203-1738, USA

Xiao-Ou Shu, and
Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, 2525 West End Ave, Suite 300, Nashville, TN 37203-1738, USA

Qi Dai
Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, 2525 West End Ave, Suite 300, Nashville, TN 37203-1738, USA

Qi Dai: qi.dai@vanderbilt.edu

Abstract

Correspondence to: Qi Dai, qi.dai@vanderbilt.edu.

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Cognitive decline is a common health problem among breast cancer patients and understanding trajectories of cognitive change following among breast cancer survivors is an important public health goal. We conducted a longitudinal study to investigate the cognitive function changes from 18 month to 3 years after breast cancer diagnosis among participants of the Shanghai Breast cancer survivor study, a population-based cohort study of breast cancer survivors. In our study, we completed cognitive function evaluation for 1,300 breast cancer survivors at the 18th month's survey and 1,059 at 36th month's survey, respectively, using a battery of cognitive function measurements. We found the scores in attention and executive function, immediate memory and delayed memory significantly improved from 18 to 36 months after breast cancer diagnosis. The improvements appeared in breast cancer survivors receiving treatments (i.e., surgery, radiotherapy, tamoxifen, or chemotherapy combined with or without tamoxifen), but not in those who received neither chemotherapy nor tamoxifen treatment. The results indicate that cognitive functions, particularly immediate verbal episodic memory, and delayed memory significantly improved among breast cancer survivors from 18 to 36 months after cancer diagnosis. In general, comorbidity was inversely associated with the improvements.

Keywords

Breast cancer; Cognitive function; Prognosis; Survival

Introduction

Advances in therapies have led to dramatic improvements in the survival rates of breast cancer survivors [1]. As a result, the 5- and 10-year relative survival rates for breast cancer are 86 and 78 %, respectively, among US women [2]. In our recent study of Chinese women with breast cancer living in Shanghai, 5-year survival rates were 88.5 % [3]. A variety of health problems associated with cancer diagnosis and its treatments, such as cognitive dysfunction, have attracted growing in attention in the research and clinical management of breast cancer survivors [4].

Cognitive dysfunction is common among breast cancer survivors [5-8] and is a serious concern for individuals both during active treatment and, thereafter, as it has the potential to substantially disrupt decision-making abilities and career, family, and social functioning more generally [6, 9]. This cognitive dysfunction, widely known as "chemobrain" represents a significant public health problem with far reaching implications [10-13]. One well-designed study found that 61 % of patients may have "chemobrain" after chemotherapy, with 50 % of patients experiencing persistent symptoms for 1 year or longer [5]. Although the exact mechanisms are not clear, possible contributors to "chemobrain" may include indirect toxicity and oxidative damage, direct injury to neurons, sex hormone changes, and inflammation associated with cancer therapies, such as radiation, chemotherapy, and hormonal therapy [14-18]. Of note, some recent studies have found signs of cognitive function improvement shortly after completing of chemotherapy [7, 19] suggesting "chemo brain" may be recoverable. However, no study has conducted to examine the trajectory of cognitive recovery long after completion of cancer treatment.

With the number of breast cancer survivors increasing, even as the duration of survival increases, understanding the cognitive function changes with time is critical for developing preventive and interventional strategies for cognitive dysfunction in breast cancer survivors. We conducted a longitudinal study to investigate the cognitive function changes from 18 months to 3 years after breast cancer diagnosis among participants of the Shanghai Breast Cancer Survivor Study (SBCSS).

Methods

Participants

The study was approved by the IRB of all the institutes involving in the study. The subjects included in this report were participants in the SBCSS, which is a population-based breast cancer survivor cohort of women who were permanent residents of Shanghai, China, and diagnosed with primary breast cancer between March 2002 and April 2006. A total of 5,042 women with newly diagnosed breast cancer and between ages 20 and 75 were recruited approximately 6 months after cancer diagnosis. Women with In situ breast cancer (accounted for only 3 % of overall breast cancer in Shanghai) were excluded from this study.

When we started to add the cognitive component in our breast cancer survival study, about two-thirds of participants completed their 18th month's follow-up survey. As a result, a total of 1,605 SBCSS participants, who were diagnosed of breast cancer between December 2004 and April 2006 and were alive at the 18th month's follow-up, were approached for the cognitive assessment during their 18th month's follow-up survey. We excluded 48 survivors from the study because they had a prior history of stroke. The remaining 1,557 breast cancer patients participated in this study.

We compared characteristics between 1,557 eligible participants with the participants in whole cohort (5,042 participants) and found that social demographics, age at cancer diagnosis, and clinical features are similar between these two study populations.

Among the 1,557 eligible participants, 1,300 (83.5 %) completed the cognitive function evaluation at the 18th month's follow-up survey. These cognitive function study participants were invited to participate in the 2nd evaluation at the 36th month's post-diagnosis survey. A total of 1,059 survivors completed the 2nd cognitive function evaluation with a response rate of 81.5 %. The reasons of non-response were refusal (216 cases, 13.9 %), moving (13 cases, 0.8 %), and other reasons (28 cases, 1.8 %) for the first evaluation, and refusal (164 cases, 12.6 %), moving (8 cases, 0.6 %), death (41 cases, 3.2 %), and other reason (28 cases, 2.2 %) for the 2nd evaluation (Fig. 1).

Data collection

At enrollment, approximately 6 months after cancer diagnosis, a face-to-face interview was administered for each eligible breast cancer case using a structured questionnaire to gather information on demographics, cancer diagnosis, menopausal statue and syndrome, comorbidity, surgery, chemotherapy, radiotherapy, tamoxifen, and other hormonal treatment, as well as Chinese traditional medicine. Among patients who ever used

tamoxifen, long-term tamoxifen users were those who were still using tamoxifen at their 36th month's visit, and short-term tamoxifen users were those who stopped using tamoxifen at the 36th month's visit. More details of clinical and lifestyle factors collection and verification were described in the papers published previously [20, 21]. Medical charts were reviewed to obtain information on tumor characteristics, include TNM stage, ER and PR status and verify cancer treatment information.

In-person interviews were administered again at 18th and 36th months after cancer diagnosis, respectively, to collect information on disease recurrence and survival status, treatment, and to capture changes in health status, including comorbidity, menopausal status, and syndrome. We asked each participant about the presence of menopausal symptoms including hot flashes, night sweats, depressed mood, vaginal dryness, and dry skin or skin dryness/itching since diagnosis and during adjuvant treatment for breast cancer at baseline interview.

Cognitive function assessment

Cognitive function was assessed using a battery comprising three widely used tools, all with robust psychometric properties: (1) a measure of immediate and delayed verbal episodic memory, the Logical Memory Subtest from the Chinese Version of the Wechsler Memory Scale [22]; (2) a measure of language/executive function (Chinese Version of the Category Fluency Test) [23]; and (3) a measure of attention/executive function (Chinese Version of the Stroop Test) [24].

Previously, we have conducted a study in Shanghai to evaluate the diagnostic validity of a short battery of cognitive tests for mild cognitive impairment and Alzheimer's disease. We selected 50 Alzheimer's disease patients (NINCDS/ADRDA criteria) and 50 mild cognitive impairment (Petersen criteria) patients who came to Huashan Hospital, Fudan University, Shanghai, China for a neurologic work-up for dementia. We also selected 50 healthy community-dwelling volunteers matched for sex and age. The initial screen included the Chinese version of the Mini-Mental State Examination. A clinical evaluation and informant-based instruments were subsequently administered. The Clinical Dementia Rating Scale was used to assess dementia severity.

We found that the logic memory subtest, category fluency test, and Stroop test were able to significantly discriminate Alzheimer's disease from mild cognitive impairment, Alzheimer's disease versus controls and mild cognitive impairment versus controls ($P < 0.05$). Age, education, and scores from the logic memory subtest, category fluency, and Stroop tests were used in multiple logistic regression models and a composite score of these variables generated. The largest area under the receiver-operator characteristic (ROC) curve was 1.00 [95 % confidence interval (95 % CI) 0.95–1.00] for Alzheimer's disease versus normal and 0.88 (95 % CI 0.79–0.94) for mild cognitive impairment versus controls. This validated battery was used in the current study.

The study interviewers, supervisors, and project director were formally trained to conduct cognitive function tests by a neurologist at the Shanghai Huashan Hospital, Fudan University [25].

Statistical methods

Demographic variables and selected characteristics were compared between subjects eligible for cognition component study and subjects who completed the examinations by the Student *t* test for continuous variables and Chi square test for dichotomous variables. Relations between age at diagnosis and scores of cognition components were measured using linear regression model. Scores of cognition components were compared by demographic variables and selected characteristics using ANOVA. Paired *t* tests were used to compare the cognition functions measured at the 18th and 36th month's visits. Statistical data analyses were performed with SAS 9.2 software (SAS Institute, Cary, NC). All of the reported *P* values were two-tailed, and statistical significance was set at $P \leq 0.05$.

Results

In Table 1, we compared the demographic variables and selected characteristics between 1,557 eligible participants, 1,300 breast cancer survivors who completed cognitive function examination at the 18th month's visit and 1,059 breast cancer survivors who completed cognitive function examination at 36th month's visit. We found that there were no significant differences between three groups on age, income, education achievements, menopausal status, menopausal syndromes at the time of being tested on cognitive function, TNM stages, ER and PR status, cancer treatments, and comorbidity of the breast cancer survivors.

We compared the cognitive functions conducted at the 18th month's visit by demographic variables and characteristics (Table 2). We found the scores of logical memory subtest test (both immediate and delayed memory), category fluency test and Stroop test were all consistently inversely correlated with age, whereas higher cognitive function scores were associated with higher income and educational achievements. After adjusting for age at diagnosis, income, and education, post-menopausal breast cancer survivors had higher scores in all of the tests than pre-menopausal women. We also found the women with earlier stage at diagnosis and use of chemotherapy had higher scores in the fluency and Stroop tests. We did not find significant differences in these cognitive measures between tamoxifen users and non-users at the 18th month.

We examined the cognitive function changes between the 18th and 36th month's visits for those who finished both cognitive assessments (Table 3). Compared to the assessment conducted at the18th month's visit, 56.58 % of women had increased scores on the immediate memory test, 49.77 % on the verbal fluency test, 56.12 % on the Stroop test, and 58.08 % on the delayed memory test at the 36th month's visit. On average, the scores of immediate memory test improved by 1.32 points (95 % CI 1.10–1.54), average scores of Stroop test improved by 1.35 points (95 % CI 0.68–2.02), and average scores of the delayed memory test increased 1.58 points (95 % CI 1.37–1.80).

Regardless of treatments (e.g., surgery, chemotherapy, radiotherapy, tamoxifen, or both chemotherapy and tamoxifen), cognitive functions including immediate memory, delayed memory, and/or Stroop tests significantly improved from 18 to 36 month after cancer diagnosis. Likewise, the long-term tamoxifen user showed the same improvement patterns.

However, for the short-term tamoxifen user, scores on the Stroop test did not significantly improve. Although sample size was substantially reduced among those who received tamoxifen but not chemotherapy, scores of immediate memory and delayed memory test significantly improved. On the other hand, breast cancer survivors who received neither chemotherapy nor tamoxifen showed no significant improvement in any of the tests. After further adjustment for age, education, income, menopausal status, depression, menopausal syndrome, TNM status, and event of relapse, the improvement pattern showed that immediate memory and delayed memory improvement were significant, but most of the significant improvement in Stroop test turned to be non-significant except the group of patients received chemotherapy. The improvements among those with tamoxifen use less than 3 years were not significant. Also, the improvement for immediate memory among those who used tamoxifen, but did not get chemotherapy was not significant after adjustment. Thus, the improvements were significant only among those who used chemotherapy or used tamoxifen more than 3 years.

Further, we conducted analyses to examine whether demographics and disease characteristics were related to the changes in cognitive function score (Table 4). After adjustment for age, education, income, menopausal status, depression, menopausal syndrome, TNM status, and event of relapse, we found that age was inversely related to the improvement of immediate memory, Fluency, and Stroop test scores but without statistics significance, and women with collage education had greater improvement in Fluency test scores comparing with women with less education. We also found, comorbidity was associated with less improvement of immediate memory.

Discussion

We found that cognitive functions, particularly short memory, attention, and executive function (tested by the Stroop test) and delayed memory significantly improved among breast cancer survivors from 18 to 36 months after cancer diagnosis. Improvements in immediate memory, delayed memory, and attention/executive were seen among survivors ever treated with surgery, radiotherapy, tamoxifen, or chemotherapy combined with or without tamoxifen. On the other hand, there were no significant improvements among those who received neither chemotherapy nor tamoxifen. We found that older age was related to less improvement in immediate memory, verbal fluency, and attention/executive. Lower educational achievement was associated with less improvement in verbal fluency test. Comorbidity seemed to be associated with less improvement in immediate memory and verbal fluency. To our best knowledge, this is the first study to investigate the long-term cognitive changes among breast cancer survivors.

Many previous studies conducted in general aging populations suggesting that age is the strongest factor associated with cognitive function and cognitive decline [26-28]. Our finding is also consistent with that from previous studies conducted among breast cancer survivors in which older age was associated with both cognitive function at baseline and cognitive function change [29-32]. A previous study found breast cancer patients who underwent both chemotherapy and hormonal therapy experienced the most severe and persistent decline in cognitive function [33], but the decline improved right after the

cessation of treatment [34]. In our study, we conducted the first cognitive function assessment at 18 months after cancer diagnosis by then most of women should have completed their cancer treatment. Because we did not have cognitive function assessment before cancer diagnosis, we could not evaluate the cognitive function decline related cancer treatment. On the other hand, we found cognitive function improvement between 18 and 36 months after cancer diagnosis, suggesting the cognitive function recovery lasted to 36 months after diagnosis. The improvements appeared among those who received treatments (i.e., surgery, radiotherapy, tamoxifen, or chemotherapy combined with or without tamoxifen), but not among those who received neither chemotherapy nor tamoxifen treatment.

The SBCSS is a population-based cohort study. We added the cognitive function component in the study after about half of participants completed the 18th month's follow-up visit. Thus, we were only able to add the component to a subset of subjects. However, we found there are no significant differences in demographic variables and selected characteristics between eligible subjects and those who participated in the cognitive function component study. Thus, selection bias is unlikely. In our study, we were unable to compare the cognitive functions between before treatment and after treatment. The temporal sequence was not clear in the analysis of the associations between demographic variables and selected characteristics and cognitive function at 18 months after diagnosis. However, we longitudinally investigated the associations of these factors with cognitive changes between the 18th and 36th month's visit. To evaluate the effect of treatments (including chemotherapy and radiotherapy) on cognitive functions is not our focus. Instead, our study focused to understand how cognitive function evolves in a long run after cancer treatment and what factors may affect these changes among long-term breast cancer survivors.

One concern is that psychomotor speed, which is commonly impaired in breast cancer survivors, cannot be evaluated by the battery we used. Thus, future studies are needed to examine the changes in psychomotor speed among breast cancer survivors. Another weakness of the study is that we did not conduct IQ assessment. Thus, we were not able to control for IQ as a potential confounding factor. Although there were 18 months between the two tests, it is still possible that practice effects contribute partially to the cognitive improvements we observed. Further studies are necessary to confirm our results.

In summary, cognitive functions, particularly short-term, attention and executive function, and long-term memory significantly improved among breast cancer survivors from the 18th- to the 36th-month after cancer diagnosis. The improvements appeared in those who received treatments, but not among those who did not receive any treatment. Future studies are warranted to not only replicate the findings, explore the unidentified predictive factors, but also understand the potential mechanism.

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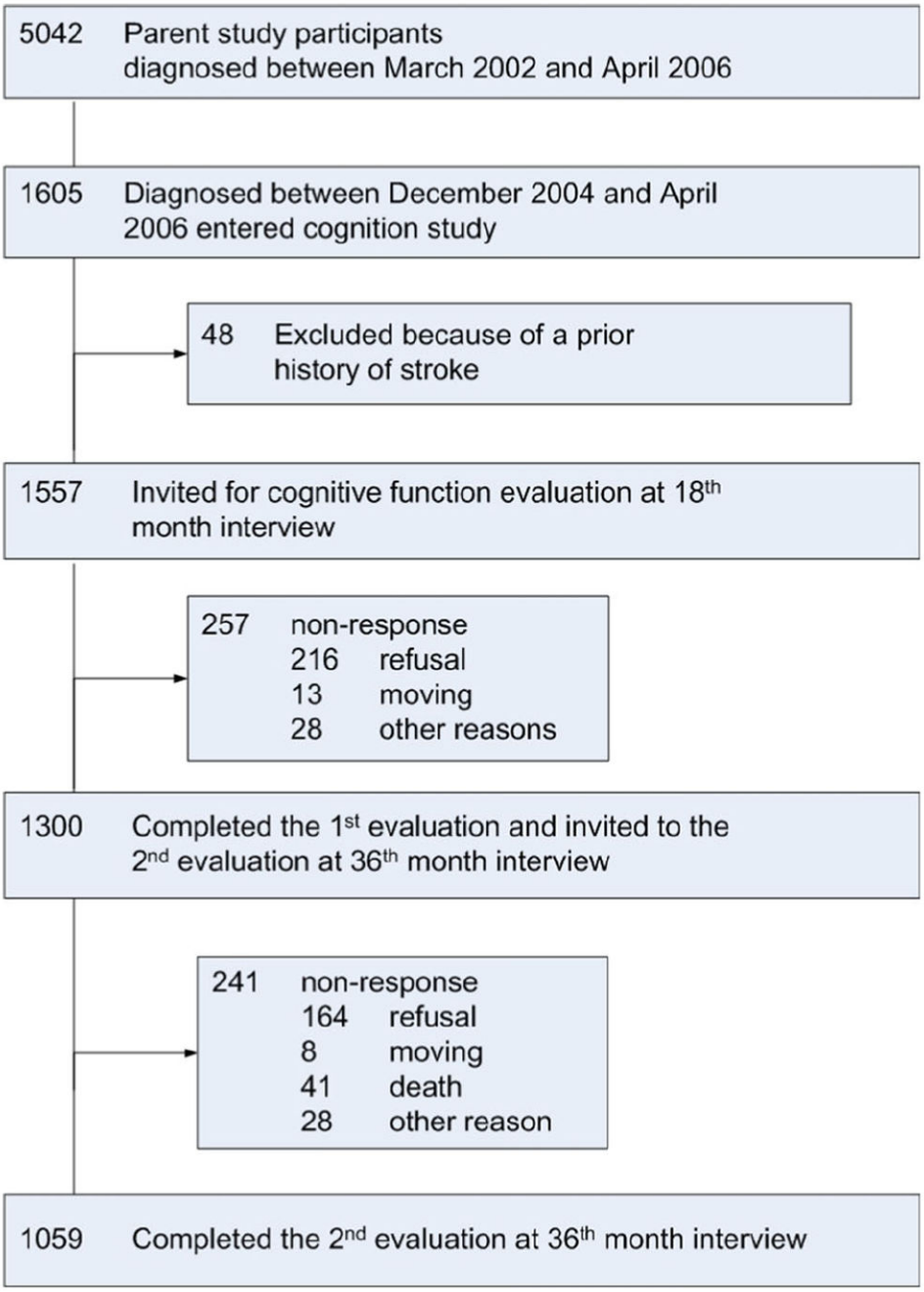

Fig. 1.
Consort diagram of Shanghai women breast cancer cohort study cognition substudy

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Table 1

Comparison of baseline characteristics between participants eligible for the cognitive study and those who completed the study

Characteristic	18th month's visit			36th month's visit	
	Participants eligible for cognition test (*n* = 1,557)	Participants finished cognition test (*n* = 1,300)	*p*[a]	Participants finished cognition test (*n* = 1,059)	*p*[b]
Age at diagnosis (years)					
Median	51.2	51.3		51.5	
Q1–Q3	47.0–59.2	47.0–59.4	0.839	47.1–59.6	0.631
Income (¥/mon/capita), %					
<1000	47.0	46.6		47.1	
1000–2000	37.9	38.9		38.4	
>2000	15.1	14.5	0.832	14.5	0.970
Education, %					
Elementary school or below	44.0	43.9		44.3	
Middle or high school	38.1	39.2		39.2	
College or above	17.9	16.9	0.752	16.5	0.960
Menopause status, %					
Pre-menopausal	47.5	47.5		46.6	
Post-menopausal	52.5	52.5	0.995	53.4	0.666
Menopausal syndromes, %					
Yes	83.0	82.6		82.9	
No	17.0	17.4	0.797	17.1	0.851
Charlsoncomorbidity index, %					
0	80.4	80.2		80.3	
≥1	19.6	19.8	0.904	19.7	0.984
TNM grade for cancer, %					
I	37.4	37.9		38.5	
IIA	34.5	34.3		34.7	
IIB	13.8	13.9		13.9	
III and above	9.5	9.0		8.3	
Unknown	4.9	4.9	0.994	4.5	0.970
ER, %					

Characteristic	18th month's visit			36th month's visit	
	Participants eligible for cognition test (*n* = 1,557)	Participants finished cognition test (*n* = 1,300)	*p*[a]	Participants finished cognition test (*n* = 1,059)	*p*[b]
Negative	34.4	33.9		33.2	
Positive	64.9	65.5		66.3	
Not known	0.7	0.6	0.914	0.5	0.836
PR, %					
Negative	43.8	43.1		43.3	
Positive	55.5	56.3		56.2	
Not known	0.7	0.6	0.879	0.5	0.892
Surgery, %					
Yes	99.6	99.5		99.5	
No	0.4	0.5	0.962	0.5	0.970
Radiology, %					
Yes	33.0	33.1		32.8	
No	67.0	66.9	0.971	67.2	0.873
Chemotherapy, %					
Yes	92.7	92.7		92.9	
No	7.3	7.3	0.959	71	0.833
Tamoxifen, %					
Yes	46.7	46.3		47.4	
No	53.3	53.7	0.837	52.6	0.611

[a] Characteristics compared between participants eligible for the cognition study and those who completed the the18th month's cognitive assessment

[b] Characteristics compared between participants who completed the 18th month's cognitive assessment and those who completed the 36th month's cognitive assessment

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Table 2

Cognitive scores at the 18th month's visit by baseline life style factors and demographics, 2003–2009

	Immediate memory			Delayed memory			Fluency			Stroop		
	Score			Score			Score			Score		
Characteristic	**Mean**[a]	**SE**[b]	***P*[c]**	**Mean**[a]	**SE**[b]	***P*[c]**	**Mean**[a]	**SE**[b]	***P*[c]**	**Mean**[a]	**SE**[b]	***P*[c]**
Age (years), β	−0.083[d]	0.013	<0.00[e]	−0.092[d]	0.013	<0.001[e]	–					
0.224[d]	0.023			<0.001[e]	–							
0.964[d]	0.053			<0.001[e]								
Monthly income (¥/person)												
<1000	9.44	0.18		8.71	0.18		40.62	0.33		73.46	0.72	
1000–2000	10.43	0.19		9.55	0.19		42.30	0.35		78.09	0.76	
>2000	11.08	0.33	<0.001	10.22	0.33	<0.001	42.88	0.61	<0.001	78.54	1.34	<0.001
Education												
Elementary school or below	8.65	0.19		7.87	0.19		39.23	0.34		69.31	0.75	
Middle or high school	10.60	0.19		9.80	0.19		42.86	0.35		79.78	0.77	
College or above	12.49	0.31	<0.001	11.55	0.31	<0.001	44.81	0.57	<0.001	84.56	1.25	<0.001
Menopausal status												
Pre-	9.44	0.21		8.58	0.21		40.89	0.39		72.75	0.86	
Post-	10.63	0.20	<0.001	9.87	0.20	<0.001	42.25	0.37	0.030	78.94	0.80	<0.001
Menopausal syndromes (at 18 **m**)												
No	9.86	0.18		9.04	0.18		41.01	0.33		73.76	0.72	
Yes	10.02	0.21	0.564	9.05	0.21	0.978	41.15	0.40	0.789	74.10	0.87	0.767
Charlson comorbidity index												
0	10.03	0.13		9.24	0.13		41.68	0.24		76.41	0.50	
≥1	10.21	0.27	0.580	9.33	0.27	0.777	41.27	0.50	0.466	74.31	1.11	0.092
TNM stage												
I	10.24	0.19		9.56	0.19		41.99	0.35		77.77	0.77	
IIA	9.97	0.20		9.02	0.20		41.14	0.37		75.17	0.81	
IIB	10.12	0.31		9.34	0.31		42.56	0.57		75.86	1.27	
III and IV	9.70	0.40		9.83	0.39		39.97	0.72		73.92	1.58	
Unknown	9.90	0.54	0.728	9.10	0.53	0.264	42.10	0.97	0.026	72.25	2.15	0.025

	Immediate memory Score			Delayed memory Score			Fluency Score			Stroop Score		
Characteristic	**Mean[a]**	**SE[b]**	***P*[c]**	**Mean[a]**	**SE[b]**	***P*[c]**	**Mean[a]**	**SE[b]**	***P*[c]**	**Mean[a]**	**SE[b]**	***P*[c]**
ER status												
Negative	9.85	0.20		8.99	0.20		41.06	0.37		76.18	0.81	
Positive	10.18	0.15		9.41	0.15		41.88	0.27		75.94	0.59	
Not known	9.82	1.49	0.416	8.20	1.48	0.181	41.54	2.73	0.199	72.35	6.04	0.811
PR status												
Negative	10.11	0.18		9.29	0.18		41.38	0.33		76.09	0.72	
Positive	10.03	0.16		9.24	0.16		41.77	0.29		75.97	0.63	
Not known	9.82	1.49	0.932	8.20	1.48	0.760	41.54	2.74	0.666	72.36	6.04	0.826
Surgery												
No	12.75	1.72		11.73	1.71		38.64	3.16		73.42	6.98	
Yes	10.06	0.12	0.119	9.25	0.12	0.149	41.61	0.22	0.348	76.01	0.47	0.711
Radiology												
No	10.11	0.15		9.32	0.14		41.73	0.27		76.15	0.59	
Yes	9.99	0.21	0.651	9.13	0.21	0.439	41.34	0.38	0.406	75.68	0.84	0.649
Chemotherapy												
No	9.80	0.46		9.04	0.46		39.74	0.83		72.09	1.84	
Yes	10.09	0.12	0.547	9.28	0.12	0.626	41.75	0.22	0.022	76.31	0.49	0.028
Tamoxifen												
No	10.06	0.16		9.19	0.16		41.26	0.29		75.60	0.65	
Yes	10.10	0.17	0.849	9.36	0.17	0.467	42.03	0.32	0.072	76.61	0.70	0.289
Use tamoxifen after 6th month												
No	9.87	0.60		8.59	0.60		40.77	1.09		76.17	2.43	
Yes	10.06	0.18	0.774	9.36	0.18	0.220	42.01	0.33	0.282	76.08	0.72	0.972

[a] Mean scores of cognitive assessment

[b] Standard errors

[c] *P* values adjusted for age at diagnosis, education and income at baseline

[d] Regression coefficients between age and cognitive score

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[e] *P* values adjusted for education and income at baseline

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Table 3

Cognitive function change from the 18 to the 36th month's assessment stratified by different treatment

	Number of participants	Mean difference	SE[a]	*P*-value	*P*-value[b]
All participants					
Immediate memory	1030	1.32	0.11	<0.001	<0.001
Delayed memory	1006	1.58	0.11	<0.001	<0.001
Fluency	1059	0.37	0.20	0.089	0.259
Stroop test	1059	1.35	0.34	<0.001	0.055
Patients received surgery					
Immediate memory	1025	1.32	0.11	<0.001	<0.001
Delayed memory	1001	1.59	0.11	<0.001	<0.001
Fluency	1054	0.37	0.20	0.098	0.270
Stroop test	1054	1.38	0.34	<0.001	0.052
Patients received chemotherapy					
Immediate memory	957	1.35	0.12	<0.001	<0.001
Delayed memory	935	1.61	0.11	<0.001	<0.001
Fluency	984	0.40	0.21	0.080	0.248
Stroop test	984	1.46	0.34	<0.001	0.043
Patients received radiotherapy					
Immediate memory	340	1.53	0.20	<0.001	<0.001
Delayed memory	334	1.81	0.20	<0.001	<0.001
Fluency	347	0.33	0.36	0.365	0.570
Stroop test	347	1.56	0.60	<0.001	0.186
Patients received tamoxifen					
Immediate memory	490	1.27	0.16	<0.001	<0.001
Delayed memory	481	1.36	0.15	<0.001	<0.001
Fluency	501	0.24	0.29	0.485	0.624
Stroop test	501	1.23	0.53	0.005	0.222
Long-term tamoxifen user					
Immediate memory	401	1.32	0.18	<0.001	<0.001
Delayed memory	393	1.40	0.17	<0.001	<0.001

	Number of participants	Mean difference	SE[a]	*P*-value	*P*-value[b]
Fluency	410	0.12	0.32	0.791	0.813
Stroop test	410	1.21	0.60	0.016	0.264
Short-term tamoxifen user					
Immediate memory	89	1.08	0.35	0.003	0.086
Delayed memory	88	1.19	0.35	<0.001	0.062
Fluency	91	0.74	0.63	0.286	0.508
Stroop test	91	1.35	1.07	0.161	0.596
Patients received both tamoxifen and chemotherapy					
Immediate memory	434	1.30	0.17	<0.001	<0.001
Delayed memory	426	1.34	0.16	<0.001	<0.001
Fluency	444	0.23	0.31	0.562	0.659
Stroop test	444	1.32	0.52	0.004	0.205
Patients received chemotherapy but no tamoxifen treatment					
Immediate memory	522	1.40	0.16	<0.001	<0.001
Delayed memory	508	1.83	0.16	<0.001	<0.001
Fluency	539	0.53	0.28	0.074	0.249
Stroop test	539	1.58	0.46	<0.001	0.112
Patients received tamoxifen but no chemotherapy					
Immediate memory	56	1.09	0.50	0.020	0.151
Delayed memory	55	1.56	0.45	0.001	0.035
Fluency	57	0.32	0.85	0.691	0.821
Stroop test	57	0.56	2.28	0.860	0.873
Patients receive neither chemotherapy nor tamoxifen treatment					
Immediate memory	17	0.47	0.42	0.235	0.661
Delayed memory	16	0.13	0.87	0.781	0.905
Fluency	18	−0.72	1.73	0.668	0.789
Stroop test	18	−2.17	1.77	0.265	0.701

[a]Standard errors

[b]Adjusted for age at diagnosis, education, income, menopausal status, depression, menopausal syndrome, TNM status, and event of relapse

Table 4

Cognitive function change from the 18 to the 36th month's assessment stratified by baseline characteristics

Characteristic	Immediate memory (*n* = 1,030)			Delayed memory (*n* = 1,006)			Fluency (*n* = 1,059)			Stroop (*n* = 1,059)		
	Mean difference	SE[a]	*P*[b]	Mean difference	SE[a]	*P*[b]	Mean difference	SE[a]	*P*[b]	Mean difference	SE[a]	*P*[b]
Age (years), β	−0.002[c]	0.018	0.908	−0.001[c]	0.020	0.945	−0.024[c]	0.032	0.443	−0.098[c]	0.055	0.076
Monthly income (¥/person)												
<1000	1.29	0.17		1.49	0.17		0.17	0.30		1.10	0.52	
1000–2000	1.29	0.18		1.69	0.18		0.38	0.32		1.99	0.56	
>2000	1.49	0.32	0.842	1.57	0.31	0.727	1.00	0.57	0.475	0.47	0.99	0.295
Education												
Elementary school or below	1.44	0.18		1.72	0.18		0.86	0.31		1.92	0.54	
Middle or high school	1.34	0.18		1.56	0.18		−0.53	0.32		1.37	0.56	
College or above	0.97	0.30	0.420	1.28	0.29	0.459	1.21	0.53	0.002	−0.23	0.93	0.160
Menopausal status												
Pre	1.52	0.21		1.69	0.21		0.93	0.37		0.95	0.64	
Post	1.14	0.19	0.250	1.48	0.19	0.533	−0.11	0.34	0.077	1.70	0.58	0.461
Charlson comorbidity index												
0	1.43	0.13		1.68	0.12		0.56	0.22		1.44	0.39	
≥1	0.86	0.26	0.049	1.16	0.26	0.070	−0.39	0.47	0.073	0.98	0.81	0.611
TNM grade for cancer												
I	1.22	0.18		1.37	0.18		0.17	0.32		1.60	0.56	
IIA	1.34	0.19		1.65	0.19		0.81	0.34		0.63	0.58	
IIB	1.69	0.30		2.01	0.30		0.12	0.54		1.10	0.93	
III and IV	0.95	0.40		1.10	0.39		0.47	0.72		2.21	1.24	
Unknown	1.52	0.55	0.565	2.47	0.53	0.089	−0.69	0.93	0.455	3.93	1.61	0.307
ER												
Negative	1.27	0.19		1.65	0.19		0.38	0.35		1.67	0.60	
Positive	1.34	0.14		1.54	0.13		0.39	0.24		1.23	0.42	
Not known	2.45	1.61	0.751	2.43	1.58	0.774	−2.58	2.91	0.595	−3.88	5.03	0.483
PR												
Negative	1.14	0.17		1.43	0.17		0.26	0.30		1.29	0.52	

Characteristic	Immediate memory (*n* = 1,030)			Delayed memory (*n* = 1,006)			Fluency (*n* = 1,059)			Stroop (*n* = 1,059)		
	Mean difference	SE[a]	*P*[b]	Mean difference	SE[a]	*P*[b]	Mean difference	SE[a]	*P*[b]	Mean difference	SE[a]	*P*[b]
Positive	1.44	0.15		1.68	0.15		0.49	0.27		1.44	0.46	
Not known	2.35	1.61	0.322	2.42	1.58	0.467	−2.58	2.91	0.510	−3.89	5.03	0.568
Surgery												
No	0.81	1.62		−0.81	1.59		2.22	2.93		−3.55	5.08	
Yes	1.32	0.11	0.754	1.59	0.11	0.132	0.36	0.20	0.528	1.37	0.34	0.333
Radiology												
No	1.22	0.14		1.48	0.14		0.47	0.25		1.39	0.43	
Yes	1.52	0.20	0.229	1.78	0.20	0.223	0.17	0.36	0.503	1.28	0.63	0.885
Chemotherapy												
No	1.16	0.44		1.30	0.44		0.65	0.79		0.68	1.36	
Yes	1.33	0.12	0.701	1.60	0.11	0.506	0.35	0.21	0.719	1.40	0.36	0.610
Tamoxifen												
No	1.38	0.15		1.77	0.15		0.49	0.28		1.37	0.48	
Yes	1.27	0.16	0.632	1.37	0.16	0.075	0.23	0.29	0.524	1.33	0.50	0.955
Chinese traditional medicine												
No	1.16	0.25		1.45	0.24		1.01	0.44		1.18	0.75	
Yes	1.36	0.12	0.469	1.61	0.12	0.555	0.21	0.22	0.101	1.40	0.39	0.799

[a] Standard errors

[b] Adjusted for age at diagnosis, education, income, menopausal status, depression, menopausal syndrome, TNM status, and event of relapse

[c] Regression coefficients between age at diagnosis and score difference