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ORIGINAL REPORT

Effects of Tamoxifen and Raloxifene on Memory and Other Cognitive Abilities: Cognition in the Study of Tamoxifen and Raloxifene

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See accompanying editorial on page 5119

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
To compare the effects of two selective estrogen receptor modulators, tamoxifen and raloxifene, on global and domain-specific cognitive function.

Patients and Methods
The National Surgical Adjuvant Breast and Bowel Project's Study of Tamoxifen and Raloxifene (STAR) study was a randomized clinical trial of tamoxifen 20 mg/d or raloxifene 60 mg/d in healthy postmenopausal women at increased risk of breast cancer. The 1,498 women who were randomly assigned in STAR were age 65 years and older, were not diagnosed with dementia, and were enrolled onto the Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) trial, beginning 18 months after STAR enrollment started. A cognitive test battery modeled after the one used in the Women's Health Initiative Study of Cognitive Aging (WHISCA) was administered. Technicians were centrally trained to administer the battery and recertified every 6 months. Analyses were conducted on all participants and on 273 women who completed the first cognitive battery before they started taking their medications.

Results
Overall, there were no significant differences in adjusted mean cognitive scores between the two treatment groups across visits. There were significant time effects across the three visits for some of the cognitive measures. Similar results were obtained for the subset of women with true baseline measures.

Conclusion
Tamoxifen and raloxifene are associated with similar patterns of cognitive function in postmenopausal women at increased risk of breast cancer. Future comparisons between these findings and patterns of cognitive function in hormone therapy and placebo groups in WHISCA should provide additional insights into the effects of tamoxifen and raloxifene on cognitive function in older women.

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INTRODUCTION

The National Surgical Adjuvant Breast and Bowel Project's Study of Tamoxifen and Raloxifene (STAR) showed that raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer and was associated with similar risk for stroke.[1] In light of similarities in efficacy between the two interventions for prevention of breast cancer, potential effects on cognition assume greater importance.

Small placebo-controlled studies have shown little effect of raloxifene on cognitive function,[2-4] although one case-control study reported a significant worsening of attention following 8 weeks of treatment with raloxifene (60 mg/d).[5] Findings from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial indicated no overall benefit of raloxifene on cognitive function[6] in women with osteoporosis. However, secondary analyses demonstrated a significant benefit of raloxifene on verbal memory and psychomotor speed in women age 70 years and older.[6] In a follow-up investigation of 5,386 women in MORE, raloxifene did not reduce the risk for Alzheimer's disease, but the 120-mg dose reduced the risk of cognitive impairment.[7] Studies of the effects of tamoxifen on cognitive function typically have

been conducted in combination with other chemotherapeutic agents or radiation therapy, and it has been difficult to determine the effects of tamoxifen alone.[8-10]

This article presents the primary results of Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR), a STAR ancillary study comparing the effects of these two selective estrogen receptor modulators (SERMs) on global and domain-specific cognitive function. On the basis of the limited data from prior studies, we hypothesized that women randomly assigned to receive raloxifene would have better cognitive performance, particularly on tests of verbal and figural memory, and less decline over time in comparison to women randomly assigned to receive tamoxifen.

PATIENTS AND METHODS

STAR Trial

STAR was a multicenter, randomized clinical trial of oral tamoxifen 20 mg/d or oral raloxifene 60 mg/d for a maximum of 5 years, among 19,747 postmenopausal women age 35 years or older at increased risk for breast cancer according to the modified Gail model.[11-12]

Co-STAR

Co-STAR enrolled 1,498 women randomly assigned in the STAR trial who were age 65 years and older and had not been diagnosed with dementia. Previous diagnoses of neurologic or psychiatric conditions, history of head injury, depression, alcohol addiction, and drug addiction were recorded but did not serve as exclusion factors for this study. All participants were fluent in English and provided written informed consent for the Co-STAR study. Co-STAR was coordinated by the Wake Forest University School of Medicine, approved by its institutional review board, and sponsored by the National Institute on Aging.

Enrollment

Co-STAR enrollment began in October 2001, 18 months after STAR enrollment started and continued until the unmasking of STAR in June 2006. Visit 1 refers to the first assessment when a participant enrolled in Co-STAR, and visits 2 and 3 refer to the beginning of years 2 and 3 in Co-STAR, respectively, corresponding to 1-year and 2-year follow-up. Each participant had a maximum of three Co-STAR assessments, which were included in this article because of the low numbers of participants with more than three visits.

Co-STAR was conducted at 153 STAR/Co-STAR clinical sites across the United States and Canada, chosen on the basis of their strong enrollment and retention in STAR and the age and ethnic distribution of participants. Co-STAR originally planned to recruit participants at their STAR randomization. However, because there was a small number of women older than age 65 years at STAR randomization, the protocol was amended to allow age-eligible women to join Co-STAR any time during their first 4 years of Co-STAR follow-up. Therefore, most participants did not receive cognitive assessments until after study drugs had been initiated. In this way, visit 1 corresponds to an on-treatment visit for 1,225 participants and to a pretreatment baseline visit for 273 women.

Co-STAR Cognitive Battery

A standardized 83-minute test battery (Table 1) modeled after the cognitive battery used in the Women's Health Initiative Study of Cognitive Aging (WHISCA)[25] was administered. The battery was designed to include measures that have been shown to be sensitive to subtle cognitive changes associated with aging and hormone therapy. Measures of verbal and figural memory were expected to show the greatest sensitivity to treatment, because WHISCA demonstrated the greatest effects of hormone therapy on these two outcomes.[25] The test battery additionally included the Modified Mini Mental State Examination (3MS) to assess global cognitive function and the Positive and Negative Affect Schedule (PANAS) and Geriatric Depression Scale to measure changes in positive affect and negative affect and depression, respectively. A description of all tests can be found online. Given that performance on memory tests improves with exposure and practice, we used a modified version of the California Verbal Learning Test (CVLT); we reduced the original number of immediate recall trials of words from a shopping list of 16 words from four semantic categories (List A) from five to three and by omitting extra category-cued recall trials. Participants were also asked to recall List A after a short and long delay (20 minutes) and to recall a second interference list (List B) before the short-delay recall. Forms with different shopping lists were also used at the third and fourth evaluations to reduce practice effects across annual evaluations.

Table 1. Summary of Test Measures and Outcome Variables

Measure	Outcome Variable	Maximum Score
Global cognitive screening[13]	Total score	100
Verbal knowledge		
PMA-V[14]	Total correct minus one third of the number incorrect	50
Verbal fluency[15]		
Letter fluency (F, A, S)	Total correct	NA
Semantic fluency (vegetables, fruits)	Total correct	NA
Figural memory		
BVRT[16,17]	Total figures with errors*	26*
Verbal memory		
CVLT[18]	Total of three List A learning trials	48
	Total for List B trial	16
	Total for short-delay trial	16
	Total for long-delay trial	16
Attention and working memory[19]		
Digits forward	Total correct trials	14
Digits backward	Total correct trials	14
Spatial ability		
Card rotations[20]	Total correct minus total incorrect	160
Fine motor speed[21]		
Finger tapping, dominant hand	Total score	NA
Finger tapping, nondominant hand	Total score	NA
Affect[22]		
PANAS-positive	Mean score	5
PANAS-negative	Mean score	5
Geriatric Depression Scale[23,24]	Total score	15

NOTE. Descriptions of tests of cognition and affect are found in Resnick et al.[25] Higher scores reflect poorer performance.

Abbreviations: PMA-V, Primary Mental Abilities-Vocabulary; NA, not applicable; BVRT, Benton Visual Retention Test; CVLT, California Verbal Learning Test; PANAS, Positive and Negative Affect Schedule.

*Plus additions of designs.

Quality assurance of the cognitive measures is described elsewhere,[25] and it included central training sessions and formal certification processes. Trained and certified technicians administered the cognitive battery at each of the 153 clinical centers.

Statistical Analysis

Four sets of statistical analyses were conducted. The first set focused on the effects of treatment on age-related changes in cognition and involved all 1,498 Co-STAR participants over 3 years, regardless of whether they had a valid pretreatment baseline assessment or not. Years 4 and 5 were excluded because data were available only for 121 and 13 participants, respectively, and analyses including year 4 were similar to those with years 1 to 3. Repeated measures analysis of covariance models included visit, treatment, and visit by treatment

Table 2. Participant Characteristics by Treatment Group for the Entire Cohort

Characteristic	Total (N = 1,498) No.	%	Tamoxifen (n = 733) No.	%	Raloxifene (n = 765) No.	%	*P*
Demographic factors							
Age, years (at Co-STAR enrollment)							
Mean	69.9		70.1		69.7		.10
SD	4.2		4.2		4.2		
65-69	878	59	417	57	461	60	.34
70-74	397	26	206	28	191	26	
75+	223	15	110	15	113	15	
Race/ethnicity							.97
Non-white	98	6	48	6	50	6	
White	1,400	94	685	94	715	94	
Education							.61
< High school	74	5	34	5	40	5	
High school graduate	409	27	191	26	218	29	
Some college	503	34	248	34	255	33	
College graduate	512	34	260	35	252	33	
Clinical factors/medical history							
Body mass index, kg/m^2							
Mean	28.8		28.4		29.2		.09
SD	9.3		6.4		11.4		
Hysterectomy	816	55	401	55	415	54	.88
Age at hysterectomy, years							
Mean	44.3		44.0		44.7		.30
SD	9.9		9.3		10.5		
Lobular carcinoma in situ	94	6	48	7	46	6	.67
Malignancy	81	5	34	5	47	6	.20
Hypertension	647	43	314	43	333	44	.77
Myocardial infarction	23	2	13	2	10	1	.47
Diabetes	110	7	56	8	54	7	.67
Depression ever	299	20	150	20	149	40	.64
Psychiatric problems ever	19	1	9	1	10	1	.89
Current use of antidepressants	226	15	101	14	125	16	.16
Years since last menstrual period							.90
1-9.9	66	4	30	4	36	5	
10-19.9	526	35	256	35	270	35	
20-29.9	555	37	271	37	284	37	
≥ 30	350	23	176	24	174	23	
3MS at first assessment							.99
≥ 95	1002	67	491	67	511	67	
90-94	337	23	165	23	172	23	
< 90	158	10	77	10	81	10	
Personal habits							
Smoking							.11
Current	80	5	48	7	32	4	
Former	578	39	284	39	294	39	
Never	826	56	395	54	431	57	
Prior usage of estrogen	1,186	79	582	79	604	79	.87
Prior usage of progestin	544	36	258	35	286	37	.37
Timing of enrollment							
Time from STAR randomization to Co-STAR enrollment, years							
Mean	2.3		2.4		2.3		.26
SD	1.6		1.6		1.6		
Follow-up							
1 year post enrollment	988	66	475	65	513	67	.36
2 years post enrollment	474	32	223	30	251	33	.32

Abbreviations: Co-STAR, Cognition in the Study of Tamoxifen and Raloxifene; SD, standard deviation; 3MS, Modified Mini Mental State Examination; STAR, Study of Tamoxifen and Raloxifene.

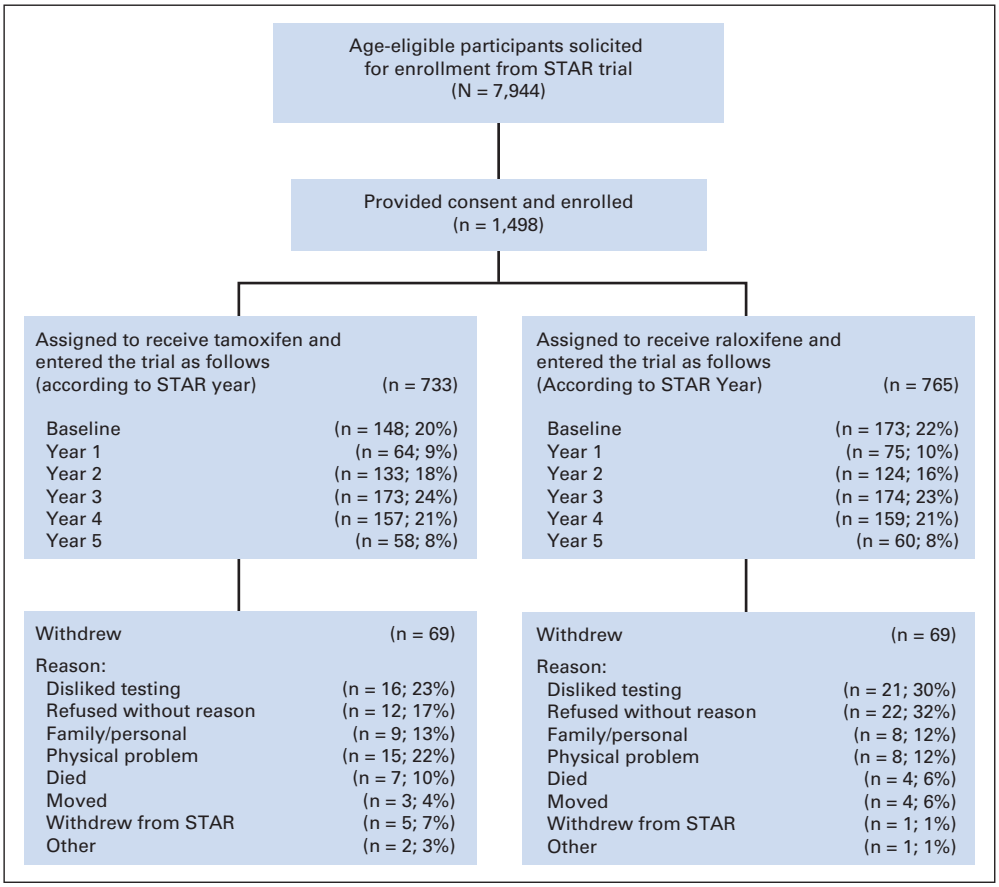

Fig 1. Cognition in the Study of Tamoxifen and Raloxifene (STAR) study flow.

interaction and were adjusted for age at Co-STAR enrollment, years between random assignment and Co-STAR enrollment, years since last menstruation, race/ethnicity, education, prior use of estrogen, and prior use of progestin (categories for last four variables are listed in Table 2). Interactions of treatment with age (< 70 *v* ≥ 70 years) and with years since last menstrual period were included to investigate differences in treatment effect by age and time since menopause. No interactions were statistically significant except age by treatment for letter fluency. *P* values for treatment and visit are reported. Models using *z* scores were fitted for CVLT to further take into account practice effects and the interaction between age and practice effects.[26] Results were similar to those of the original models (data not shown).

The second set of analyses focused on changes from pre- to post-treatment for 273 participants who completed the first cognitive battery before they started taking their medication. These analyses included visit, treatment, and their interaction and were adjusted for age at Co-STAR enrollment, race/ethnicity, education, and baseline scores for the cognitive test. These analyses were repeated replacing race and education with prior use of estrogen and prior use of progestin, and similar results were obtained. Characteristics for both cohorts are listed in Tables 2 and 4.

Finally, analyses were repeated with 1,227 participants who completed the first tests after starting their medication and with 450 participants who completed all three visits; repeat analyses showed similar results to the first analyses (data not shown). A significance level of .01 was adopted a priori for all outcomes to control for multiple outcomes; a Bonferroni adjustment would have been too strict, given the correlation among these outcomes.

RESULTS

Of the 7,944 age-eligible STAR participants, 733 previously randomly assigned to receive tamoxifen and 765 randomly assigned to receive raloxifene were enrolled in Co-STAR (Fig 1). Three-hundred and twenty-one participants (21%) entered Co-STAR at the same time they entered STAR. Of these, 273 had their first Co-STAR visit before they started their medication. The remainder entered the trial after they started their medication up to 5 years after STAR began. Sixty-nine participants withdrew from each arm during the trial for reasons including a dislike of cognitive testing; family, personal, or physical problems; and, rarely, death.

No statistically significant differences in baseline demographic factors, clinical factors/medical history, personal habits, or the timing of enrollment were detected between the two treatment groups (Table 2). The average age (standard deviation) of the cohort at the time of Co-STAR enrollment was 69.9 (4.2) years ranging from 65 to 83 years, and 60% of women had had their last menstrual period more than 20 years ago. The majority were white (94%) and 68% had attended at least some college. More than half (55%) reported that they had undergone a hysterectomy, with 79% reporting prior usage of estrogen. Hypertension was fairly prevalent (43%), and 20% had experienced depression. 3MS scores at the first assessment were ≥ 95 for 67% of the participants. Only 5% reported current smoking. On average, there was a 2.3-year interval between STAR random assignment and Co-STAR enrollment. Approximately two thirds of the participants returned for a 1-year follow-up after Co-STAR enrollment, and one third had 2-year follow-up assessments, because some women had already completed their participation in STAR.

No differences in mean cognitive measures between treatment groups were statistically significant at the initial assessment (data

not shown). There were no significant differences in adjusted mean cognitive scores between the two treatment groups across visits. However, CVLT List B interference scores, reflecting difficulty learning a new word list after having been exposed to the primary word list, tended to be higher in the raloxifene group than in the tamoxifen group ($P = .04$) (Table 3). Letter fluency scores were significantly higher in women younger than age 70 years (40.7 ± 0.5) in the raloxifene group compared with older women (37.8 ± 0.7), but not in the tamoxifen group, 39.0 ± 0.6 and 39.3 ± 0.7, respectively. Scores for global cognition, verbal and visual memory, visuospatial skills, verbal knowledge, PANAS-positive, and general depression changed significantly over the course of the study independently of treatment. Performance improved over time on the 3MS, Benton Visual Retention Test, card rotations, Primary Mental Abilities-Vocabulary, and Geriatric Depression Scale ($P \leq .01$). CVLT scores generally improved from visit 1 to visit 2 and then declined at visit 3 ($P < .0001$); for the majority of women, the decline at visit 3 coincided with the introduction of a more difficult alternate form. Evidence that the form was more difficult comes from WHISCA, where the placebo group showed a significant decrease in performance on that form. We controlled for form effect by repeating these analyses for the subset of 450 women who completed all three visits and for the 1,225 women whose first cognitive test session was conducted after random assignment and found similar results.

The 273 women who had their first Co-STAR evaluation completed before starting their medication were similar by treatment group, except that 46% of women in the raloxifene group had used progestin compared with 31% in the tamoxifen group (Table 4). These women also tended to be younger ($P = .01$), were more likely to have undergone a hysterectomy ($P = .01$), to have reported prior estrogen usage ($P = .01$), and to have hypertension ($P = .0002$) or diabetes ($P = .002$) than the remaining 1,225 participants (data not shown).

Analysis of the baseline cognitive scores revealed statistically significant group differences only for PANAS-positive affect ($P = .01$: Table 5) with higher positive mean scores for the raloxifene group (3.6) than for the tamoxifen group (3.4). Across two follow-up years (Table 5), there were no significant treatment differences in adjusted means for any of the measures. There was a trend ($P = .06$) for the raloxifene group to show higher positive affect than the tamoxifen group. In addition, there were some significant time effects across the two follow-up years with the most notable effects occurring for the CVLT measures, where scores declined from

Table 3. Mean (SE) Scores for Cognitive and Affective Measures, by Treatment Group and Visit (N = 1,498)

	Visit													
	1				2				3					
	Tamoxifen (n = 733)		Raloxifene (n = 765)		Tamoxifen (n = 475)		Raloxifene (n = 513)		Tamoxifen (n = 223)		Raloxifene (n = 251)		*P*	
Measure	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Treatment	Visit
Global cognition														
3MS	96.3	0.12	96.3	0.12	96.9	0.13	97.0	0.12	96.9	0.17	97.2	0.15	.61	< .0001
Verbal knowledge														
PMA-V	35.8	0.33	36.1	0.33	37.0	0.35	37.1	0.34	37.6	0.40	37.7	0.39	.71	< .0001
Verbal fluency														
Letter fluency	38.7	0.44	38.8	0.43	39.7	0.49	40.2	0.47	39.4	0.60	40.5	0.57	.56*	< .0001
Semantic fluency	29.0	0.22	29.2	0.22	29.1	0.25	29.2	0.25	29.2	0.33	29.1	0.31	.69	.96
Memory														
BVRT errors	6.8	0.14	6.8	0.14	6.4	0.16	6.3	0.16	6.3	0.21	5.9	0.20	.70	< .0001
CVLT														
Total List A trials	28.0	0.23	28.4	0.22	29.2	0.26	29.6	0.25	25.8	0.34	27.0	0.32	.10	< .0001
Total List B trials	6.3	0.08	6.5	0.07	6.5	0.09	6.7	0.09	4.7	0.13	4.9	0.12	.04	< .0001
Short-delay free recall	8.4	0.11	8.3	0.11	8.8	0.13	8.9	0.13	8.0	0.17	8.2	0.16	.93	< .0001
Long-delay free recall	8.9	0.11	8.9	0.11	9.4	0.13	9.5	0.12	9.2	0.16	9.4	0.16	.86	< .0001
Attention and working memory														
Digits forward	7.8	0.08	7.6	0.08	7.7	0.09	7.7	0.09	7.9	0.11	7.6	0.11	.10	.88
Digits backward	6.8	0.08	6.7	0.07	6.9	0.09	6.7	0.08	6.8	0.11	6.6	0.11	.08	.28
Spatial ability														
Card rotations	57.9	1.04	57.7	1.02	63.2	1.15	63.6	1.11	65.5	1.41	64.6	1.35	.93	< .0001
Fine motor speed														
Finger tapping, dominant	40.8	0.29	41.2	0.29	40.9	0.33	41.2	0.32	41.4	0.42	41.6	0.41	.31	.18
Finger tapping, nondominant	38.2	0.25	38.6	0.24	38.3	0.28	38.4	0.27	38.0	0.34	38.7	0.33	.24	.95
Affect														
PANAS-positive	3.6	0.03	3.7	0.02	3.6	0.03	3.6	0.03	3.6	0.04	3.6	0.04	.45	.01
PANAS-negative	1.5	0.02	1.6	0.02	1.5	0.03	1.6	0.03	1.6	0.03	1.5	0.03	.40	.64
GDS	1.4	0.08	1.4	0.07	1.5	0.09	1.4	0.09	1.7	0.12	1.6	0.11	.68	.01

NOTE. Scores were adjusted for age, ethnicity, education, prior estrogen use, prior progestin use, and time since last menstrual period.
Abbreviations: SE, standard error of the mean; 3MS, Modified Mini Mental State Examination; PMA-V, Primary Mental Abilities-Vocabulary; BVRT, Benton Visual Retention Test; CVLT, California Verbal Learning Test; PANAS, Positive and Negative Affect Schedule; GDS, Geriatric Depression Scale.
*Age by treatment interaction ($P = .01$).

Table 4. Participant Characteristics by Treatment Group for Participants With True Baseline Measure

Characteristic	Total (n = 273) No.	%	Tamoxifen (n = 128) No.	%	Raloxifene (n = 145) No.	%	*P*
Demographic factors							
Age, years (at Co-STAR enrollment)							
Mean	69.4		69.5		69.3		.56
SD	3.4		3.4		3.4		
65-69	173	63	79	62	94	65	.86
70-74	76	28	37	29	39	27	
75+	12	9	12	9	12	8	
Race/ethnicity							.74
Non-white	24	10	9	7	15	10	
White	7	3	2	2	5	3	
Education							.58
< High school	15	5	6	5	9	6	
High school graduate	90	33	45	35	45	31	
Some college	75	27	38	30	37	26	
College graduate	93	34	39	30	54	37	
Clinical factors/medical history							
Body mass index, kg/m^2							.29
Mean	28.8		29.2		28.4		
SD	6.8		7.8		5.7		
Hysterectomy	167	61	81	63	86	59	.50
Age at hysterectomy, years							
Mean	45.1		44.3		45.8		.33
SD	10.4		10.0		10.8		
Lobular carcinoma-in-situ	15	5	5	4	10	7	.28
Malignancy (non-breast)	18	7	6	5	12	8	.23
Hypertension	146	53	66	52	80	55	.55
Myocardial infarction	7	3	4	3	3	2	.58
Diabetes	32	12	19	15	13	9	.13
Depression ever	56	21	25	20	31	21	.71
Psychiatric problems ever	2	1	0	0	2	1	.35*
Years since last menstrual period							.45
1-9.9	54	20	28	22	26	18	
10-19.9	44	16	26	21	18	13	
20-29.9	18	7	8	6	10	7	
≥ 30	9	3	2	2	7	5	
3MS at first assessment							.52
≥ 95	189	69	86	67	103	71	
90-94	54	20	29	23	25	17	
< 90	130	11	13	10	17	12	
Personal habits							
Smoking							.35
Current	11	4	7	6	4	3	
Former	105	39	45	35	60	42	
Never	154	57	75	59	79	55	
Prior use of estrogen	233	85	104	81	129	89	.07
Prior use of progestin	106	39	40	31	66	46	.02
Timing of enrollment							
Time from STAR randomization to Co-STAR enrollment, years							
Mean	1.1		1.1		1.1		.95
SD	0.2		0.2		0.2		
Follow-up							
1 year post enrollment	264	97	124	97	140	97	.88
2 years post enrollment	176	64	83	65	93	64	.90

Abbreviations: Co-STAR, Cognition in the Study of Tamoxifen and Raloxifene; SD, standard deviation; 3MS, Modified Mini Mental State Examination; STAR, Study of Tamoxifen and Raloxifene.
*On the basis of Fisher's exact test.

Table 5. Baseline Mean (SE) Cognitive Measures and Mean Change From Baseline (SE) by Years Since Co-STAR Enrollment and Treatment Group

	Pretreatment Baseline Visit 1				Visit 2				Visit 3				*P*	
	Tamoxifen (n = 128)		Raloxifene (n = 145)		Tamoxifen (n = 124)		Raloxifene (n = 140)		Tamoxifen (n = 83)		Raloxifene (n = 93)			
Measure	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Treatment	Visit
Global cognition														
3MS	94.9	0.59	95.0	0.54	0.26	0.33	0.48	0.31	−0.26	0.40	1.06	0.38	.11	.85
Verbal knowledge														
PMA-V	30.8	1.26	29.7	1.17	1.08	0.41	1.12	0.38	1.20	0.47	1.70	0.45	.68	.25
Verbal fluency														
Letter fluency	34.6	1.63	34.0	1.51	1.34	0.64	0.95	0.60	1.29	0.75	1.51	0.71	.83	.61
Semantic fluency	27.8	0.83	27.8	0.77	0.48	0.42	0.03	0.40	−0.51	0.50	−0.56	0.47	.56	.03
Memory														
BVRT errors	7.9	0.55	8.1	0.51	−0.48	0.30	−0.40	0.28	−0.73	0.34	−1.41	0.32	.62	.003
CVLT														
Total List A trials	28.4	0.86	28.5	0.80	1.51	0.43	1.51	0.40	−3.31	0.50	−1.89	0.48	.31	< .0001
Total List B trials	6.2	0.28	6.5	0.26	0.19	0.16	0.29	0.15	−1.56	0.19	−1.74	0.18	.96	< .0001
Short-delay free recall	8.2	0.44	8.1	0.40	0.59	0.21	0.46	0.20	−0.96	0.25	−0.36	0.24	.60	< .0001
Long-delay free recall	9.0	0.41	8.8	0.38	0.67	0.21	0.44	0.20	−0.23	0.25	0.10	0.24	.93	.001
Attention and working memory														
Digits forward	7.2	0.30	6.9	0.28	−0.02	0.15	0.01	0.14	−0.02	0.18	−0.08	0.17	.98	.70
Digits backward	6.6	0.27	6.1	0.26	0.18	0.14	−0.19	0.14	−0.16	0.17	−0.27	0.16	.13	.08
Spatial ability														
Card rotations	58.4	3.87	62.6	3.59	7.16	1.69	8.00	1.58	6.10	1.97	5.40	1.86	.90	.17
Fine motor speed														
Finger tapping, dominant	39.8	1.16	40.3	1.07	0.08	0.56	−0.33	0.52	0.26	0.65	−0.04	0.63	.60	.61
Finger tapping, nondominant	37.7	0.97	38.6	0.89	0.06	0.44	−0.02	0.41	−0.18	0.50	−0.45	0.48	.79	.31
Affect														
PANAS-positive	3.4	0.10	3.6	0.09	−0.12	0.05	0.01	0.05	−0.10	0.06	−0.04	0.05	.06	.69
PANAS-negative	1.8	0.09	1.7	0.08	0.07	0.05	0.03	0.04	0.00	0.06	−0.06	0.05	.40	.07
GDS	2.0	0.29	1.9	0.27	0.30	0.16	0.14	0.15	0.57	0.19	0.13	0.18	.15	.43

NOTE. Adjusted for age, ethnicity, education, and baseline measure, for participants with true baseline measures (N = 273).
Abbreviations: SE, standard error of the mean; Co-STAR, Cognition in the Study of Tamoxifen and Raloxifene; 3MS, Modified Mini Mental State Examination; PMA-V, Primary Mental Abilities-Vocabulary; BVRT, Benton Visual Retention Test; CVLT, California Verbal Learning Test; PANAS, Positive and Negative Affect Schedule; GDS, Geriatric Depression Scale.

follow-up year 1 to follow-up year 2 ($P \leq .001$) because a more difficult test form was introduced.

DISCUSSION

In Co-STAR, we hypothesized that raloxifene would confer comparatively greater cognitive benefits, particularly in the domain of verbal memory. Contrary to our hypothesis, there were no significant differences in cognitive test performance between raloxifene and tamoxifen groups. The lack of a robust difference between the two treatments was evident in all 1,498 enrolled women and in an analysis restricted to 273 women with pretreatment baseline data. The only trend observed for cognitive measures was that raloxifene was associated with higher scores compared with tamoxifen ($P = .04$) on the List B interference trial, one of four verbal memory measures in the analysis involving all 1,498 women. Overall, these results demonstrated no significant differences in the effect of tamoxifen versus raloxifene on global or domain-specific cognitive function.

In contrast to this study, modest cognitive benefits were observed with raloxifene in the MORE trial, which examined cognitive function in 7,478 women with osteoporosis randomly assigned to receive raloxifene at 60 or 120 mg/d or placebo.[6] Over a 3-year period, there were no overall differences in cognitive function between women randomly assigned to receive either dose of raloxifene versus placebo in a sample with a mean age of 66 years. There was a trend in the overall sample ($P = .05$) for women randomly assigned to receive raloxifene to have a reduced risk of cognitive impairment on verbal memory. In addition, secondary analyses restricted to women age 70 years and older demonstrated a significant benefit of raloxifene on verbal memory and psychomotor speed in MORE. Given that Co-STAR participants were recruited to be age 65 years and older, we hypothesized that raloxifene would confer cognitive benefits compared with tamoxifen. Although the raloxifene group showed a trend to better performance than the tamoxifen group on the List B outcome of the CVLT, this finding was not confirmed in the subset of women with a pretreatment baseline. Therefore, our findings did not support this hypothesis. Although 59% of the Co-STAR sample was younger than age 69 years and thus would not be expected to enjoy the possible age-related benefit of raloxifene, we observed only one interaction between treatment and age (< 70 *v* ≥ 70 years) suggesting improved fluency with raloxifene in younger versus older women. Also importantly, in MORE, raloxifene was compared with placebo, whereas in Co-STAR raloxifene was compared with tamoxifen.

Several other differences between Co-STAR and MORE are worth considering. More than 4,000 women in the MORE trial completed pre- and post-treatment cognitive assessments, leading to greater power to detect an effect of raloxifene on cognitive function, especially if that effect was greatest from baseline to 1-year post-treatment. Second, unlike Co-STAR participants, all MORE participants had osteoporosis. A strong risk factor for osteoporosis is estrogen deficiency.[27] Conversely, early menses and older age at first birth—two factors in the Gail model for determination of breast cancer risk—are associated with higher levels of estrogen. In preclinical studies, raloxifene in the absence of estradiol exerted partial agonist effects in the hippocampus, but in the presence of estrogen, it exerted mixed agonist/antagonist effects.[28] The hippocampus is a critical structure in mediating verbal memory[29] and the effects of estrogen compounds, including raloxifene, on memory.[30-32] Thus, raloxifene may have different effects on tasks mediated by the hippocampus such as verbal memory in women with low estrogen compared with women with higher estrogen, such that greater cognitive benefits may be evident in women with low estrogen. Another difference between MORE and Co-STAR was that in Co-STAR, there was only a 60 mg/d dose of raloxifene, whereas in MORE, there were doses of 60 and 120 mg/d.

Earlier observational studies provided mixed evidence concerning the effects of tamoxifen on cognition. Previous clinical studies provided some suggestion that tamoxifen might produce impairments in cognitive function. For example, a study of women with breast cancer found that those receiving treatment with chemotherapy and tamoxifen performed worse than women receiving chemotherapy alone on tests of visual memory and visuospatial function.[8] Conversely, in a cross-sectional study of early-stage breast cancer, anastrozole led to significant impairments in verbal and visual learning and memory compared with tamoxifen.[33] In a cross-sectional study of elderly nursing home patients, women treated with tamoxifen showed a reduced risk of Alzheimer's disease, improved activities of daily living, and improved decision making.[34] To our knowledge, Co-STAR is the first clinical trial to examine the effects of tamoxifen on cognitive function in healthy women, and no significant differences were observed between tamoxifen and raloxifene.

The study has two important limitations. First, there was no placebo arm for comparison with the tamoxifen and raloxifene treatment arms. If both tamoxifen and raloxifene had beneficial or adverse effects on memory in Co-STAR, then cognitive effects would not be evident. Therefore, we cannot rule out the possibility that either or both treatments would have positive or negative effects on cognition when compared with placebo. Second, only a minority (approximately 20%) of participants completed assessments at baseline and throughout the trial, resulting in low power to detect treatment effects occurring within the first year of treatment. Notably, Co-STAR has several strengths. The results address the important clinical issue of whether cognitive effects should be considered when choosing between two SERMs that show similar efficacy in preventing breast cancer.[1] The test battery was the same as that used in the Women's Health Initiative Memory Study,[25] which will allow for comparisons of tamoxifen and raloxifene with placebo and conjugated equine estrogen with and without medroxyprogesterone acetate.

In summary, the present findings indicate that tamoxifen and raloxifene are associated with similar patterns of cognitive function in healthy postmenopausal women at increased risk of breast cancer. These findings will help women and their health care providers make more informed decisions regarding the use of tamoxifen or raloxifene for the prevention of breast cancer, because the data do not support one SERM conferring a cognitive advantage over the other. These results, however, should be interpreted with caution because of the absence of a placebo group. Future comparisons between these findings and patterns of cognitive function in hormone therapy and placebo groups in WHISCA should provide further insights into the effects of tamoxifen and raloxifene on cognitive function in older women.

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