

## COGNITIVE FUNCTION IN POSTMENOPAUSAL WOMEN TREATED WITH RALOXIFENE

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FOR THE MULTIPLE OUTCOMES OF RALOXIFENE EVALUATION INVESTIGATORS

**ABSTRACT**

**Background** In postmenopausal women, estrogen may have a beneficial effect on cognition or reduce the risk of decline in cognitive function. Whether raloxifene, a selective estrogen-receptor modulator, might have similar actions is not known.

**Methods** As part of the Multiple Outcomes of Raloxifene Evaluation trial, we studied 7478 postmenopausal women with osteoporosis (mean age, 66 years), who were enrolled at 178 sites in 25 countries. The women were randomly assigned to receive raloxifene (60 mg or 120 mg) or placebo daily for three years. We compared the mean scores of the groups on six tests of cognitive function, which were administered at base line and at six months and one, two, and three years. Women were classified as having a decline in cognitive function if the change in their scores at three years was in the worst 10 percent.

**Results** The mean cognitive scores in the three groups of women were similar at base line. The scores improved slightly in all three groups during the three-year study period, with no significant differences among the groups. The risk of decline in the cognitive function, as measured by four of the six tests, did not differ significantly between the two raloxifene groups combined and the placebo group, but there was a trend toward less decline in the combined raloxifene group on the two tests of verbal memory (relative risk, 0.77) and attention (relative risk, 0.87). Newly reported or worsening hot flashes did not negatively influence test scores or the effect of treatment on test performance.

**Conclusions** Raloxifene treatment for three years does not affect overall cognitive scores in postmenopausal women with osteoporosis. (N Engl J Med 2001; 344:1207-13.)

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**E**STROGEN receptors are located throughout the brain, especially in regions that are involved in learning and memory, such as the hippocampus and amygdala.<sup>1</sup> In animals, estrogen increases cholinergic and serotonergic activity and stimulates neuronal growth<sup>2</sup>—effects that could benefit cognition. Whether estrogen has beneficial effects on cognition in older women is controversial.<sup>3</sup> Some observational studies suggest that estrogen therapy may improve cognition in postmenopausal women, particularly verbal memory and attention,<sup>4,5</sup> but the results of randomized trials of the effects of estrogen on cognition in postmenopausal women are conflicting.<sup>6-15</sup>

Raloxifene is a selective estrogen-receptor modulator used for the prevention<sup>16</sup> and treatment<sup>17</sup> of postmenopausal osteoporosis. Raloxifene stimulates neurite outgrowth in cultured cells<sup>18</sup> and increases choline acetyltransferase activity in the hippocampus of ovariectomized rats<sup>19</sup>—an effect that may be associated with improvements in cognition.<sup>20</sup> On the other hand, raloxifene increases the incidence of hot flashes in women,<sup>17,21</sup> and hot flashes have been postulated to be associated with poorer cognitive performance.<sup>22</sup>

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial evaluated the effect of a three-year regimen of raloxifene in a total of 7705 postmenopausal women with osteoporosis (we report on the results in 7478 of the women here). We administered cognitive tests to these women to determine whether raloxifene treatment affected cognition or the risk of a decline in cognitive function.

**METHODS****Study Subjects and Design**

We studied the 7705 postmenopausal women with osteoporosis who were enrolled in the MORE trial at 180 sites in 25 countries. The primary outcomes of that trial were vertebral fractures and bone mineral density; cognitive function was a secondary outcome. All the women had been postmenopausal for at least two years. The details of the study design and additional criteria for inclusion and exclusion have been reported previously.<sup>17</sup> The protocol was approved by the human-studies review board at each site, and all the women gave written informed consent.

The women were randomly assigned to receive either 60 mg or 120 mg orally of raloxifene per day, or oral placebo. Eli Lilly supplied randomly numbered kits containing raloxifene and placebo tablets that appeared identical; the trial centers distributed the kits to the women in numerical order. Each woman received two tablets daily: two placebo tablets, one placebo tablet and one 60-mg tablet of raloxifene, or two 60-mg tablets of raloxifene. The women were also supplied with and asked to take calcium (500 mg) and vitamin D (400 to 600 IU) daily.

**Characteristics of the Women**

At base line, we collected information on the age, race or ethnic background, educational level, smoking status, alcohol consumption, medical conditions, previous use or nonuse of postmenopausal therapy, reproductive history, height, and weight of the enrolled women. We documented the incidence of new or worsening hot flashes, as reported by the women at base line and at subsequent

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visits. During the study, both the women's reports of amnesia, confusion, and dementia and instances of these conditions as identified by the investigators were recorded. We recorded the ingestion of other drugs, including sedative-hypnotic, anxiolytic, anticholinergic, and antidepressant drugs. The Geriatric Depression Scale,<sup>23</sup> a self-administered scale that assesses depressive symptoms during the past week, was administered at base line and at subsequent visits. The scores on this scale range from 0 to 15, with higher scores indicating greater depression.

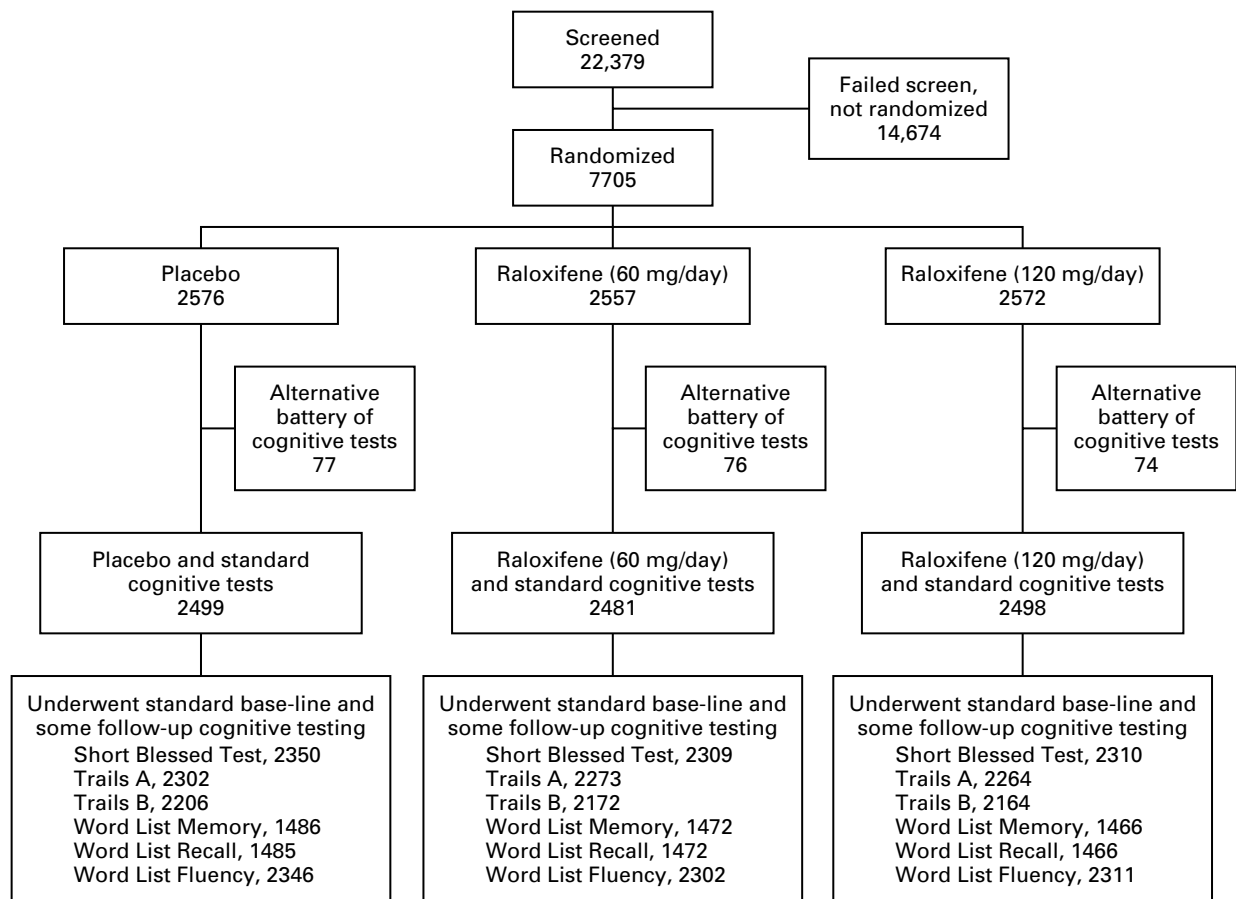
**Tests of Cognitive Function**

Six tests of cognitive function, similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease,<sup>24</sup> were administered at base line and at six months and one, two, and three years in a standard order by trained study personnel who were unaware of the women's treatment-group assignments. At two study sites in the United States, 227 women underwent a different battery of cognitive tests, the results of which are not included here. The 7478 women enrolled at the remaining 178 sites underwent the cognitive testing discussed in this report (Fig. 1).

The Short Blessed Test<sup>25</sup> assesses orientation, concentration, and memory. Scores range from 0 to 28, with lower scores indicating better performance. The Trail Making Test, Parts A and B (referred to hereafter as Trails A and B) measure visuospatial scanning, sequential processing, motor speed, executive function, and attention.<sup>26</sup> The tasks in these tests involve connecting a series of con-

secutively numbered circles (in Trails A, which has a greater focus on attention) or an alternating sequence of numbered and lettered circles (in Trails B, which has a greater focus on executive function). Shorter times to completion (in seconds) indicate better performance. The Word List Memory and Recall tests<sup>24</sup> measure learning, immediate memory, and delayed memory. The memory test requires the immediate recall of 10 standardized words. The recall test involves the recollection of the 10 words learned previously after a delay of approximately 20 minutes. Scores for both tests range from 0 to 10, with higher scores indicating better performance. The Word List Fluency Test<sup>27</sup> measures verbal production, semantic memory, and language; in this test subjects name as many animals as possible in 60 seconds. Higher scores indicate better performance. The Short Blessed, Trails A and B, and Word List Fluency tests were administered at all 178 sites. Validated versions of the Word List Memory and Word List Recall tests are available only in English, French, and Spanish, which limited their use to 4424 women.

We defined cognitive decline in relative terms, as a change in the cognitive score from base line to three years that was in the worst 10 percent. This definition has previously been reported to provide a sensitive and specific measure of dementia in a group of elderly women.<sup>28</sup> For elderly women, especially those in non-English-speaking countries, the validity of education-based definitions of cognitive decline is uncertain,<sup>29</sup> and definitions that use the study cohort as a reference are preferred. To determine whether this def-



**Figure 1.** Enrollment and Cognitive Testing of Postmenopausal Women with Osteoporosis in the Multiple Outcomes of Raloxifene Evaluation Trial.

inition was robust, we also conducted analyses in which we defined cognitive decline as a change in score indicating decline that was more than 2 SD greater than the mean change in score.

**Statistical Analysis**

All statistical analyses were performed with the use of SAS software (version 6.08, SAS Institute, Cary, N.C.). The primary analysis was an intention-to-treat comparison, by means of an analysis of covariance, of the mean cognitive-test scores at three years, with adjustment for the base-line test scores. We imputed data for missing follow-up scores by carrying the last observation forward. Test scores were then compared between treatment groups over time with a repeated-measures analysis of covariance including only the data that were available at each follow-up visit, with adjustment for base-line scores.

Additional prespecified analyses included the risk of decline in cognitive function as measured by each test and the influence of hot flashes on test scores. With the placebo group used as the reference group, the relative risk of a decline in cognitive function as measured by each test, with its 95 percent confidence interval, was calculated for women assigned to raloxifene (with the 60-mg and 120-mg groups combined). An analysis of covariance was used to compare the test scores at three years (adjusted for age, treatment assignment, and base-line cognitive score) for women who had new or worsening hot flashes at any time after randomization with the scores of women who did not have new or worsening hot flashes. We then included a term for the interaction between hot flashes and treatment group in the model to determine whether the reporting of hot flashes modified the effect of raloxifene on test scores. Since age is the greatest predictor of cognitive decline, we used an analysis of covariance to perform a post hoc sub-

group analysis in which we divided the women evenly into three age groups and compared cognitive-test scores at three years (adjusted for base-line scores) among the treatments within each age group.

Reports of amnesia, confusion, and dementia were compared among the treatment groups with the use of Pearson's chi-square test (in instances in which there were 10 or more events reported) or Fisher's exact test (in instances in which there were 5 to 9 events reported). All statistical tests were two-sided.

**RESULTS**

The mean age of the women in the study was 66 years (range, 31 to 80); the average number of years of education was 12; and 28 percent of the women had taken estrogen previously. The base-line characteristics of the women in the three treatment groups were similar (Table 1).

There were no significant differences among the three treatment groups in the mean scores on any of the cognitive tests at base line or after three years of treatment (Table 2). The percentage of women who underwent any cognitive testing at three years was 78 percent in the placebo group, 80 percent in the 60-mg raloxifene group, and 81 percent in the 120-mg raloxifene group (P=0.01). The women who did not complete the three years of treatment tended to be older (a mean of 67 years, as compared with 66 years among those who completed treatment; P<0.001) and to

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE 7478 POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS.\***

CHARACTERISTIC	60 mg OF RALOXIFENE (N=2481)	120 mg OF RALOXIFENE (N=2498)	PLACEBO (N=2499)	P VALUE†
Age (yr)	66±7	66±7	66±7	0.41
Years since menopause	19±9	19±8	19±8	0.37
Education (yr)	12±4	12±4	12±4	0.72
Depression score‡	1.3±2.0	1.4±2.0	1.3±2.0	0.89
Body-mass index§	25±4	25±4	25±4	0.98
Previous hysterectomy (%)	24	22	22	0.23
Previous estrogen therapy (%)	29	28	28	0.66
Alcohol use (>3 drinks/wk) (%)	18	17	17	0.61
Current smoker (%)	17	17	17	0.97
Medical history (%)				
Hot flashes	4	4	4	0.84
Myocardial infarction	2	2	2	0.35
Stroke	0	0	1	0.12
Depression	9	8	8	0.50
Use of CNS-affecting drugs (%)				
Anxiolytic	8	9	7	0.16
Antidepressant	5	5	5	0.60
Sedative-hypnotic	5	6	5	0.21
Anticholinergic	2	2	3	0.24

\*Plus-minus values are means ±SD. CNS denotes central nervous system.

†P values are from an analysis of variance for continuous data and Pearson's chi-square test for categorical data.

‡Scores are from the Geriatric Depression Scale, short version; scores range from 0 to 15, with higher scores indicating greater depression.

§The body-mass index is the weight in kilograms divided by the square of the height in meters.

**TABLE 2.** MEAN ( $\pm$ SE) COGNITIVE-TEST SCORES AT BASE LINE AND AT THREE YEARS IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS ASSIGNED TO RALOXIFENE OR PLACEBO.\*

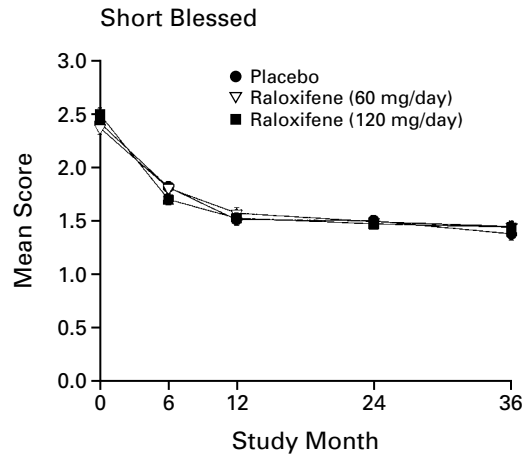
COGNITIVE TEST	60 mg OF RALOXIFENE	120 mg OF RALOXIFENE	PLACEBO	P VALUE†
<b>Short Blessed</b>				
Base line	2.4 $\pm$ 0.1	2.5 $\pm$ 0.1	2.4 $\pm$ 0.1	0.54
3 yr	1.5 $\pm$ 0.1	1.5 $\pm$ 0.1	1.5 $\pm$ 0.1	0.78
<b>Trails A</b>				
Base line	53.8 $\pm$ 0.6	53.5 $\pm$ 0.6	53.4 $\pm$ 0.6	0.94
3 yr	46.2 $\pm$ 0.5	46.6 $\pm$ 0.5	47.3 $\pm$ 0.5	0.06
<b>Trails B</b>				
Base line	104.1 $\pm$ 0.9	104.1 $\pm$ 0.9	104.0 $\pm$ 0.9	0.99
3 yr	96.0 $\pm$ 0.9	96.7 $\pm$ 0.9	95.8 $\pm$ 0.9	0.57
<b>Word List Memory</b>				
Base line	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	7.2 $\pm$ 0.0	0.89
3 yr	8.3 $\pm$ 0.0	8.3 $\pm$ 0.0	8.3 $\pm$ 0.0	0.74
<b>Word List Recall</b>				
Base line	7.0 $\pm$ 0.1	7.0 $\pm$ 0.1	7.1 $\pm$ 0.1	0.88
3 yr	8.3 $\pm$ 0.1	8.3 $\pm$ 0.1	8.2 $\pm$ 0.1	0.14
<b>Word List Fluency</b>				
Base line	18.6 $\pm$ 0.1	18.6 $\pm$ 0.1	18.7 $\pm$ 0.1	0.65
3 yr	19.9 $\pm$ 0.1	19.8 $\pm$ 0.1	19.9 $\pm$ 0.1	0.57

\*The number of women included in the analyses for each test is given in Figure 1. For the Short Blessed Test and Trails A and B, lower scores indicate better performance; for the Word List Memory, Word List Recall, and Word List Fluency tests, higher scores indicate better performance.

†P values are from an analysis of covariance with adjustment for baseline cognitive score.

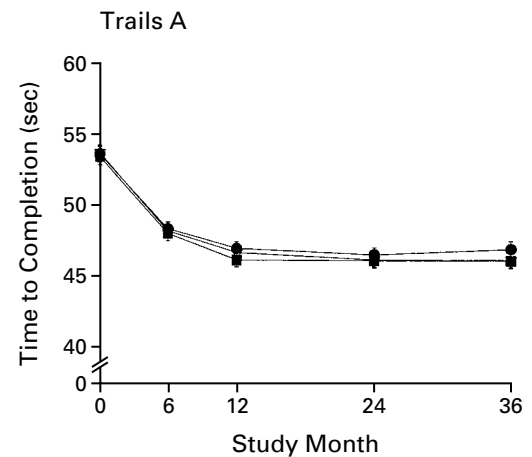
have lower cognitive-test scores at base line ( $P < 0.05$  for all cognitive tests). Analysis of the cognitive-test scores of the women who did not complete the study revealed no statistically significant differences according to treatment-group assignment. Furthermore, the results of an analysis including only women who completed the study and were at least 80 percent compliant in taking study medication and the results of an analysis including only women in countries where English is the principal language were similar to those in the intention-to-treat analysis. According to a repeated-measures analysis of only the data that were available for each visit, the mean scores improved during the first year in all treatment groups ( $P < 0.05$  for all tests); however, there were no significant differences among treatment groups for any test at any visit (Fig. 2). There was no significant difference in mean ( $\pm$ SD) depression scores at three years (placebo group,  $1.2 \pm 2.0$ ; 60-mg raloxifene group,  $1.3 \pm 2.0$ ; 120-mg raloxifene group,  $1.3 \pm 2.1$ ;  $P = 0.69$ ), and adjusting the cognitive-test scores for the depression scores did not change the results.

The risk of decline in cognitive function, as measured by four of the six cognitive tests, did not differ significantly between women in the combined raloxifene group and women in the placebo group (Table 3); all women classified as having cognitive decline had lower scores at three years than at base line. The women who took raloxifene tended to have a lower



NO. OF WOMEN TESTED

Placebo	2472	2325	2253	2070	1875
Raloxifene (60 mg/day)	2449	2285	2210	2051	1917
Raloxifene (120 mg/day)	2470	2282	2234	2072	1942

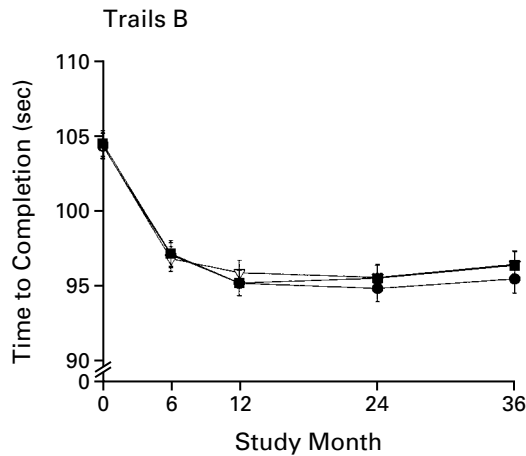


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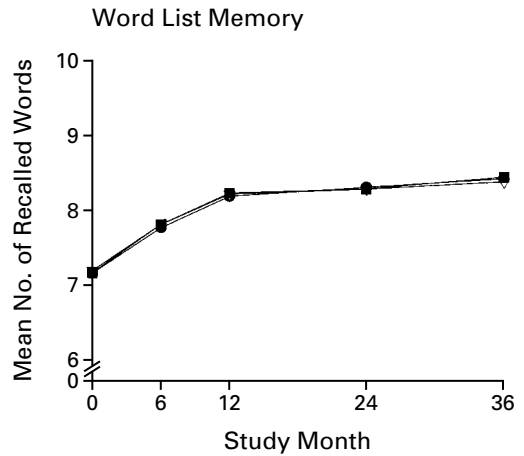
Placebo	2422	2314	2240	2055	1855
Raloxifene (60 mg/day)	2411	2274	2199	2037	1905
Raloxifene (120 mg/day)	2418	2274	2218	2060	1925

**Figure 2.** Mean ( $\pm$ SE) Scores on Tests of Cognitive Function in Postmenopausal Women with Osteoporosis in the Two Raloxifene Groups and the Placebo Group.

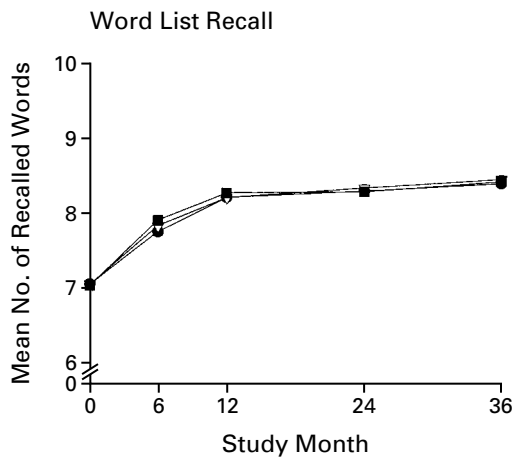
For the Short Blessed Test and Trails A and B, lower scores indicate better performance; for the Word List Memory, Word List Recall, and Word List Fluency tests, higher scores indicate better performance.



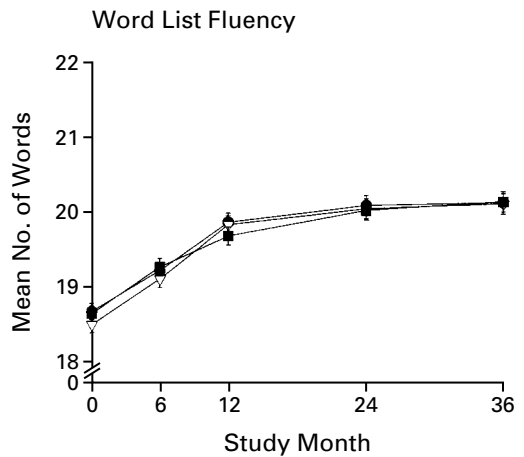
NO. OF WOMEN TESTED					
Placebo	2330	2226	2188	2000	1809
Raloxifene (60 mg/day)	2309	2192	2140	1988	1855
Raloxifene (120 mg/day)	2315	2190	2161	2006	1874



NO. OF WOMEN TESTED					
Placebo	1573	1473	1416	1287	1182
Raloxifene (60 mg/day)	1571	1459	1406	1283	1213
Raloxifene (120 mg/day)	1585	1452	1416	1300	1212



NO. OF WOMEN TESTED					
Placebo	1572	1471	1416	1283	1180
Raloxifene (60 mg/day)	1571	1455	1404	1281	1205
Raloxifene (120 mg/day)	1584	1450	1414	1297	1211



NO. OF WOMEN TESTED					
Placebo	2472	2325	2254	2060	1871
Raloxifene (60 mg/day)	2441	2283	2207	2045	1917
Raloxifene (120 mg/day)	2467	2286	2234	2067	1937

risk of decline in cognitive function as measured by the Word List Recall test (relative risk, 0.77; 95 percent confidence interval, 0.59 to 1.00;  $P=0.05$ ) and by Trails A (relative risk, 0.87; 95 percent confidence interval, 0.74 to 1.02;  $P=0.09$ ). The difference between the proportion of the women in the combined raloxifene group and the proportion in the placebo group in whom there was a decline in cognitive function was 1.4 percentage points according to the scores on the Word List Recall test (number needed to treat

to prevent 1 case of cognitive decline, 71) and 1.3 percentage points according to the scores on Trails A (number needed to treat, 83). The results were similar when the analyses were limited to women who completed the study and when cognitive decline was defined as a change in the score indicating decline that was more than 2 SD worse than the mean change.

As expected, test scores at three years, adjusted for base-line scores, were poorest in the oldest subgroup of women (those older than 70 years of age;  $P<0.05$

**TABLE 3. RISK OF DECLINE IN COGNITIVE FUNCTION DURING THE THREE-YEAR TRIAL IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS ASSIGNED TO RALOXIFENE OR PLACEBO.\***

COGNITIVE TEST	RELATIVE RISK WITH RALOXIFENE (95% CI)†	P VALUE
Short Blessed	1.05 (0.87–1.27)	0.63
Trails A	0.87 (0.74–1.02)	0.09
Trails B	1.07 (0.92–1.25)	0.39
Word List Memory	1.03 (0.88–1.22)	0.70
Word List Recall	0.77 (0.59–1.00)	0.05
Word List Fluency	0.97 (0.81–1.15)	0.72

\*Women were classified as having a decline in cognitive function if the change in their cognitive test scores at three years was in the worst 10 percent.

†The relative risks are for a decline in cognitive function in the combined raloxifene group as compared with the placebo group. CI denotes confidence interval.

for the comparisons between women older than 70 years and those 70 years old or younger on all cognitive tests). Among women 70 years old or younger, there were no differences between treatment groups in the scores on any test. Among women older than 70 years, there were no differences between treatment groups in the scores on four of the six tests; however, the women who took raloxifene performed slightly better than those who took placebo on the Word List Recall test (score, 7.6 vs. 7.4;  $P=0.02$ ) and on Trails A (time, 52 seconds vs. 54 seconds;  $P=0.01$ ).

More women in the combined raloxifene group (10.7 percent) than in the placebo group (6.3 percent,  $P<0.001$ ) reported new or worsening hot flashes during the study. Test scores at three years, adjusted for age, base-line scores, and treatment assignment, did not differ significantly between women with and women without hot flashes, except for Trails A, in which women with hot flashes performed slightly better than those without them (45 seconds vs. 47 seconds,  $P=0.03$ ). There was no evidence of a differential treatment effect between women who reported hot flashes and those who did not ( $P$  for the interactions  $>0.05$ ).

There were no statistically significant differences in the frequency of reported amnesia, confusion, or dementia (2.8 percent in the placebo group, 3.2 percent in the 60-mg raloxifene group, and 3.4 percent in the 120-mg raloxifene group;  $P=0.52$ ). Dementia was reported in a total of 20 women (0.3 percent) and did not differ in frequency among the treatment groups ( $P=0.95$ ).

## DISCUSSION

The results of this large, randomized, controlled trial of the effect of a selective estrogen-receptor mod-

ulator on cognition in postmenopausal women revealed no significant differences between the treatment groups in performance on cognitive tests at three years, although the women who received raloxifene tended to have a slightly lower risk of decline in cognitive function as measured by tests of verbal memory and attention. These results extend the findings of a smaller, short-term trial in which raloxifene had no consistent effect on cognitive function in 143 postmenopausal women.<sup>30</sup> The lack of an overall effect of raloxifene on cognitive scores at three years is also consistent with the results of several trials of estrogen in postmenopausal women. The results of 10 randomized, controlled studies of the effect of estrogen therapy on the performance of postmenopausal women without dementia on tests of cognitive function have been reported.<sup>6–15</sup> There were no consistent effects on cognition in three trials,<sup>11,13,15</sup> whereas improvement on some tests of cognition, particularly on those assessing verbal memory and attention, were found in other trials.<sup>6–10,12,14</sup>

Our finding that raloxifene tended to reduce the risk of a decline in cognitive function, as measured by tests of verbal memory and attention, could actually be due to chance, since we performed multiple comparisons. However, previous studies have suggested that estrogen may selectively improve cognition in these areas.<sup>9,12,14</sup> Raloxifene, and also possibly estrogen, may not affect overall cognition in relatively young postmenopausal women without symptoms, but it may protect against the development of cognitive impairment. A meta-analysis of prospective and case-control studies found a 30 percent reduction in the risk of Alzheimer's disease in women taking estrogen.<sup>3</sup> Although we did not perform a clinical evaluation of the women who had a decline in cognitive function, we used a conservative criterion for cognitive decline that is sensitive and specific for the detection of dementia in older women.<sup>28</sup>

There were similar improvements in cognitive scores among the women in all the treatment groups during the first year of the trial, suggesting an effect of learning or practice. Improvements of similar magnitude were reported previously for most of these tests in studies in which subjects without dementia underwent repeated cognitive assessments over the course of one year.<sup>24</sup> Such results highlight the importance of placebo-controlled trials, which make it possible to distinguish treatment effects from practice or learning effects.

The women in our study had few menopausal symptoms; however, hot flashes were reported more frequently among the women assigned to raloxifene than among those assigned to placebo. Hot flashes, along with the night sweats and sleep disturbances that can accompany them, have been postulated to impede performance on cognitive testing.<sup>22</sup> However, regardless of treatment, cognitive scores were no worse in wom-

en who had hot flashes than in those who did not, and raloxifene did not affect cognitive scores differently in women who reported hot flashes and those who did not. These results are consistent with those of an observational study that found similar cognitive performance in women with more severe symptoms and in those with less severe symptoms.<sup>31</sup> The results do not support the hypothesis that hot flashes impede cognitive performance in postmenopausal women.

Treatment with raloxifene for three years does not have an overall effect on cognitive function in postmenopausal women with osteoporosis. There was some evidence in our study that raloxifene may lower the risk of a decline in verbal memory and attention, but further studies are required to confirm these findings.

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