Relative Effects of Tamoxifen, Raloxifene, and Conjugated Equine Estrogens on Cognition

Mark A. Espeland, Ph.D.,¹ Sally A. Shumaker, Ph.D.,¹ Marian Limacher, M.D.,² Stephen R. Rapp, Ph.D.,¹ Therese B. Bevers, M.D.,³ David H. Barad, M.D., M.S.,⁴ Laura H. Coker, Ph.D.,¹ Sarah A. Gaussoin, M.S.,¹ Marcia L. Stefanick, Ph.D.,⁵ Dorothy S. Lane, M.D., M.P.H.,⁶ Pauline M. Maki, Ph.D.,⁷ and Susan M. Resnick, Ph.D.,⁸ for the WHIMS and CoSTAR Study Groups

Abstract

Objective: To compare the relative effects of conjugated equine estrogens (CEE), raloxifene, and tamoxifen therapies on cognition among women aged ≥ 65 years.

Methods: Annual Modified Mini-Mental State (3MS) examinations were used to assess global cognitive function in the two randomized placebo-controlled clinical trials of CEE therapies of the Women's Health Initiative Memory Study (WHIMS) and the Cognition in the Study of Tamoxifen and Raloxifene (CoSTAR). Analyses were limited to women who had 3MS testing at baseline and the first 3 years of follow-up and, because of potential ethnic-related differences between studies, to Caucasian women (WHIMS $n = 6211$, CoSTAR $n = 250$). Covariate adjustment was used to compare the postrandomization mean 3MS scores among the three active therapies with placebo therapy while controlling for differences between groups with respect to dementia risk factors.

Results: At baseline, the average (SD) 3MS scores by group were 95.24 (4.28) for placebo, 95.19 (4.33) for CEE, 94.60 (4.76) for raloxifene, and 95.02 (4.03) for tamoxifen. Compared with placebo, each active therapy was associated with a small mean relative deficit in 3MS scores of ≤ 0.5 units, which was fairly consistent between women with and without prior hysterectomy. Relative deficits were slightly greater for tamoxifen ($p = 0.001$) and less marked for raloxifene ($p = 0.06$) and CEE ($p = 0.02$) therapies. Relative deficits appeared to be greater among women with lower baseline 3MS scores: $p = 0.009$ (tamoxifen), $p = 0.08$ (raloxifene), and $p = 0.03$ (CEE).

Conclusions: Although unmeasured differences between trials may have confounded analyses, these findings raise the possibility that both tamoxifen and raloxifene adversely affect cognitive function in older women; however, the magnitude of the effect is small, and the long-term consequences are unknown.

Introduction

THE STUDY OF TAMOXIFEN AND RALOXIFENE (STAR) reported that these two agents yielded similar breast cancer risk reductions and recommended that raloxifene be adopted as a first-line therapy for cancer prevention based on better tolerability.¹ Within the full trial, no material differences in self-reported forgetfulness or mental health were found between the two drugs.² Its ancillary study on cognition, Cognition in the study of Tamoxifen and Raloxifene (CoSTAR),

found that women assigned to the two agents had similar cognitive profiles over time.³ Because a placebo arm was not included in the STAR trial, these results do not address how raloxifene and tamoxifen may affect cognition compared with nontreatment.

Two placebo-controlled studies have reported that the 60 mg/day dose of raloxifene used in STAR has little effect on cognitive test scores or incident cognitive impairment in women with osteoporosis.⁴⁻⁶ No placebo-controlled clinical trials evaluating tamoxifen's impact on cognition have been

¹Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

²University of Florida, Gainesville, Florida.

³MD Anderson Cancer Center, University of Texas, Houston, Texas.

⁴Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine Bronx, New York.

⁵Center for Disease Prevention Research, Stanford University, Palo Alto, California.

⁶Department of Preventive Medicine, Stony Brook University School of Medicine, Stony Brook, New York.

⁷Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois.

⁸Laboratory of Personality and Cognition/03, Gerontology Research Center, NIA, NIH, Baltimore, Maryland.

published; however clinical and preclinical studies describe both potentially adverse^{7–11} and beneficial^{12–15} effects on cognition and brain function.

This article describes exploratory analyses that pool cognitive data from CoSTAR with those of the Women's Health Initiative Memory Study (WHIMS), which consisted of two large placebo-controlled clinical trials of postmenopausal hormone therapy. CoSTAR and WHIMS shared many design features, including age range, measurement protocols, and time frame.^{16,17} Both programs included annual assessments of global cognitive function with the Modified Mini-Mental State (3MS) examination.¹⁸ We focus on the subset of women in these trials whose cognitive assessments began at baseline. By aligning women according to measured dementia risk factors, we develop cross-trial estimates of the relative effects of tamoxifen and raloxifene on global cognition compared with placebo and hormone therapy.

Materials and Methods

CoSTAR volunteers were recruited from the STAR breast cancer prevention trial,^{1,2} in which women were randomly assigned to 20 mg/day oral tamoxifen or 60 mg/day oral raloxifene. Women eligible for STAR had a 5-year predicted breast cancer risk of $\geq 1.66\%$,¹⁹ were at least 35 years of age, were postmenopausal, and had not taken postmenopausal hormone therapy, tamoxifen, raloxifene, oral contraceptives, or androgens for at least 3 months. Additional exclusion criteria were based on competing risks (e.g., history of stroke, pulmonary embolism, deep vein thrombosis, uncontrolled diabetes, or hypertension).¹ CoSTAR began enrolling women 18 months after STAR enrollment had started, beginning in October 2001, and collected annual batteries of cognitive outcomes, including 3MS examinations.³ STAR enrollment ceased in November 2004. Women aged ≥ 65 years were eligible to join CoSTAR any time during their first 4 years of CoSTAR follow-up; most did not have baseline cognitive assessments. Enrollment in CoSTAR continued until the unmasking of STAR in June 2006. Analyses described in this report are limited to the 274 (18.3%) of 1498 CoSTAR women who were enrolled in CoSTAR at STAR baseline and who had at least one follow-up 3MS.

WHIMS tested the relative effect of 0.625 mg/day conjugated equine estrogens (CEE) alone and in combination with 2.5 mg/day of the progestin medroxyprogesterone acetate (CEE+MPA) on the incidence of probable dementia and, secondarily, global cognitive function and other cognitive outcomes. Its study design, eligibility criteria, and recruitment procedures have been reported previously.^{16,17} Volunteers aged 65–80 years were recruited from the Women's Health Initiative (WHI) hormone trials beginning in June 1996. These women were randomly assigned with equal probability to active therapy (CEE-alone if prior hysterectomy, CEE+MPA if no hysterectomy) or matching placebo. A 3-month washout from any current hormone therapy was required before baseline evaluation. Exclusion criteria were based on competing risks (medical conditions with a predicted survival of < 3 years), safety (e.g., prior breast cancer at any time or breast cancer suspected at baseline screening, other invasive cancer within the past 10 years except nonmelanoma skin cancer, low hematocrit or platelet count), adherence and retention factors (e.g., dementia, unwillingness or inability to

complete study requirements, alcoholism, adherence during a pill run-in), and probable dementia. Analyses in this article are limited to the 7168 (95.8% of 7479) women enrolled in WHIMS for which a baseline 3MS test (i.e., within 6 months of randomization) was recorded and who had at least one follow-up 3MS test.

The National Institutes of Health and Institutional Review Boards for all participating institutions approved protocols and consent forms. Informed written consent was obtained from all participants.

Cognitive assessment

The 3MS test consists of 15 items, the sum of which ranges between 0 and 100. Higher scores reflect better cognitive functioning.¹⁸ Test items measure temporal and spatial orientation, immediate and delayed recall, executive function, naming, verbal fluency, abstract reasoning, praxis, writing, and visuoconstructional abilities. The 3MS test has good reliability, sensitivity, and specificity for detecting cognitive impairment and dementia.²⁰ 3MS tests were administered by trained and certified technicians who were masked to treatment assignment and other outcomes. Technicians for both trials were centrally trained by staff and investigators at the Wake Forest University Coordinating Center according to similar protocols.

Baseline demographic and clinical factors were collected with self-report and standardized assessments. Factors included in our analyses were those collected in a similar manner in both studies: age, education, ethnicity, body mass index (BMI), hypertension, diabetes, and prior hysterectomy. Weight was measured to the nearest 0.1 kg, and height was recorded to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by the square of height in meters.

Follow-up and retention

After discovery of an unfavorable risk/benefit ratio of its noncognitive end points for CEE+MPA therapy, the WHI trial of this regimen was discontinued in July 2002.²¹ The WHI trial of CEE-alone therapy was discontinued in February 2004 because of an increased risk of stroke and embolic events and the lack of any favorable effect on cardiovascular disease (CVD) for CEE-alone therapy.²² These decisions discontinued the WHIMS trials. Mean follow-up for women included in our analyses was 4.6 (range 1–8) years, and at annual follow-up examinations, 96.4% (year 1), 97.4% (year 2), and 98.7% (year 3) of expected women provided 3MS data. The STAR study was unmasked April 30, 2006, at which time women were informed of study results. Attendance at annual examinations was 96.3% (year 1), 87.1% (year 2), and 77.8% (year 3) of expected for women included in this report. Because only 15 CoSTAR women who were enrolled at baseline had an on-trial year 4 examination, these data were excluded from analyses.

Statistical analysis

Pooling data across clinical trials is complicated because the separate eligibility criteria, recruitment processes, and study objectives produce cohorts that may differ according to many measured and unmeasured attributes. Covariate adjustment with respect to risk factors for cognitive impairment is necessary to reduce biases. We used tests of interactions to assess

the comparability of risk factor relationships with baseline 3MS between trial cohorts. Factors for which relationships were similar between trials were used as covariates in all comparisons. Factors for which relationships did not appear to be similar were used to stratify analyses. 3MS scores were left-skewed; to address this, inference was based on transformed data calculated as the logarithm of 102 minus the score.²³ Generalized linear models were used to contrast longitudinal postrandomization transformed 3MS scores, with adjustment for baseline 3MS and dementia risk factors.²⁴ Means and confidence intervals (CIs) were reported for scores back-transformed to original units. Participants were analyzed according to their assigned therapy. Because WHIMS found little difference in how CEE and CEE+MPA affect 3MS scores²⁵ and because this comparison is not a feature of this article, data from the two WHIMS hormone therapy trials were pooled. As the adverse effect of hormone therapy on

3MS scores in the WHIMS trial was greatest among women whose baseline scores were lower,^{25,26} analyses were repeated in the subset of women with baseline 3MS <95 (i.e., >1 SD less than a perfect score) to estimate the effects of tamoxifen and raloxifene in women with some evidence of pretrial cognitive deficits. The *p* values from pairwise comparisons of treatment groups that we report are not adjusted for multiple comparisons in our exploratory analyses.

Results

Characteristics of WHIMS and CoSTAR women at the time of enrollment into their parent WHI and STAR trials were balanced with respect to treatment assignment within each trial (Table 1). However, differences between trial cohorts with respect to many of the characteristics are evident. Compared with WHIMS women, CoSTAR women tended to

TABLE 1. CHARACTERISTICS OF WHIMS AND CoSTAR WOMEN AT ENROLLMENT INTO WHI AND STAR TRIALS: GROUPED ACCORDING TO TREATMENT ASSIGNMENT

Baseline characteristic	WHIMS n (%)		CoSTAR n (%)		Between trials <i>p</i> value ^a
	CEE therapy n = 3528	Placebo n = 3640	Raloxifene n = 145	Tamoxifen n = 129	
Age, years					
65–69	1626 (46.1)	1684 (46.3)	94 (64.8)	80 (62.0)	<0.001
70–74	1271 (36.0)	1293 (35.5)	39 (26.9)	37 (28.7)	
75+	631 (17.9)	663 (18.2)	12 (8.3)	12 (9.3)	
Education					
<High school graduate	265 (7.5)	270 (7.4)	9 (6.2)	6 (4.7)	<0.001
High school graduate	761 (21.7)	823 (22.7)	45 (31.0)	45 (34.9)	
Some college	1461 (41.6)	1422 (39.2)	37 (25.5)	39 (30.2)	
College graduate	1027 (29.2)	1110 (30.6)	54 (37.2)	39 (30.2)	
Ethnicity					
American Indian	14 (0.4)	12 (0.3)	2 (1.4)	1 (0.8)	0.0004
Asian	63 (1.8)	58 (1.6)	6 (4.1)	4 (3.1)	
African American	251 (7.1)	253 (7.0)	5 (3.4)	2 (1.6)	
Hispanic/Latina	83 (2.4)	84 (2.3)	0 (0.0)	1 (0.8)	
White	3066 (86.9)	3171 (87.1)	130 (89.7)	120 (93.0)	
Other	51 (1.4)	62 (1.7)	2 (1.4)	1 (0.8)	
BMI, kg/m ²					
≤24.9	999 (28.4)	1080 (29.9)	40 (27.6)	40 (31.5)	0.96
25.0–29.9	1275 (36.3)	1303 (36.1)	62 (42.8)	37 (29.1)	
30.0–34.9	765 (21.8)	814 (22.5)	25 (17.2)	32 (25.2)	
≥35.0	476 (13.5)	417 (11.5)	18 (12.4)	18 (14.2)	
Hypertension					
No	1714 (48.9)	1841 (50.9)	65 (44.8)	63 (48.8)	0.29
Yes	1788 (51.1)	1775 (49.1)	80 (55.2)	66 (51.2)	
Diabetes					
No	3230 (91.7)	3338 (91.8)	132 (91.0)	110 (85.3)	0.05
Yes	294 (8.3)	297 (8.2)	13 (9.0)	19 (14.7)	
Hysterectomy					
Yes	1390 (39.4)	1420 (39.0)	86 (59.3)	82 (63.6)	<0.001
No	2138 (60.6)	2220 (61.0)	59 (40.7)	47 (36.4)	
3MS group					
<90	361 (10.2)	347 (9.5)	20 (13.8)	12 (9.3)	0.25
90–94	807 (22.9)	836 (23.0)	35 (24.1)	36 (27.9)	
95–100	2360 (66.9)	2457 (67.5)	90 (62.1)	81 (62.8)	
3MS mean (SD)					
All women	95.19 (4.33)	95.24 (4.28)	94.60 (4.76)	95.02 (4.03)	0.33
White women	95.75 (3.78)	95.79 (3.68)	95.25 (3.97)	95.18 (4.02)	0.14

^aChi-square test or analysis of variance.

WHIMS, Women's Health Initiative Memory Study; CoSTAR, Cognition in the Study of Tamoxifen and Raloxifene; CEE, conjugated equine estrogens.

be younger and were less likely to have a college education, less likely to be from an ethnic minority, less likely to have diabetes, and more likely to have had a hysterectomy. The distributions of obesity and the prevalences of hypertension were similar between the two trials. The baseline mean 3MS (SD) scores of the four treatment groups also appear in Table 1. These did not differ significantly between trials, and their cumulative distributions were nearly identical (Fig. 1).

At baseline, age-adjusted associations of 3MS scores with education, BMI, hypertension, and diabetes status appeared to be fairly similar in the two study cohorts (nonsignificant tests of interactions) (Table 2). Relationships that 3MS scores had with hysterectomy status differed between trials ($p = 0.046$), so that results of analyses stratified by hysterectomy status are presented. Because of small cell sizes, there was little power to detect between-trial differences in relationships that 3MS scores had with ethnicity, for which the trial's distributions differed markedly. Because of this, we focused this report on analyses limited to Caucasian participants (87% of WHIMS women; 91% of CoSTAR women), whose baseline mean 3MS scores are shown in Table 1. We also conducted analyses using the full cohort with covariate adjustment for the most prevalent ethnic groups; these yielded comparable results and are not reported.

Most women in this CoSTAR cohort had only 2 or fewer years of follow-up (Table 3). Follow-up rates did not vary by treatment assignment. Among these WHIMS women, follow-up of ≤ 2 years was more common among women who were older or less educated or had diabetes (all $p < 0.05$). Because of the earlier termination of the CEE + MPA trial, follow-up was shorter for women without prior hysterectomy. In this CoSTAR cohort, none of these relationships approached statistical significance. Table 3 provides fitted mean 3MS scores (from the log-transformed data), with adjustment for baseline 3MS, age, education, BMI, hypertension, and diabetes

status. These estimates were from Caucasian participants and stratified by hysterectomy status. The log-transformation, by reducing the skew, yielded means that were greater than raw averages. Adjusted 3MS means were slightly lower among women assigned to active therapies compared with the WHIMS placebo at most time points. When averaged across follow-up, these did not reach statistical significance for women without prior hysterectomy (overall, $p = 0.18$): 97.56 (95% CI 97.49-97.63, placebo), 97.48 (97.40-97.55, (hormone therapy), 97.32 (96.78-97.80, raloxifene), and 97.16 (96.56-97.69, tamoxifen). For women with prior hysterectomy, differences among arms were ordered similarly and reached statistical significance ($p = 0.007$). Pairwise (unadjusted for multiple comparisons) p values contrasting active therapies with placebo were $p = 0.10$ (hormone therapy), $p = 0.09$ (raloxifene), and $p = 0.003$ (tamoxifen). The adjusted means were 97.29 (97.19-97.38, placebo), 97.17 (97.06-97.27 hormone therapy), 96.89 (96.41-97.34, raloxifene), and 96.55 (96.02-97.04, tamoxifen). Figure 2 portrays these differences as mean deficits from the perfect score of 100.

Because patterns appeared similar, an analysis was conducted that included women both with and without a uterus (with hysterectomy status as a covariate). Treatment groups means were 97.46 (97.40-97.52, placebo), 97.36 (97.30-97.42, hormone therapy), 97.14 (96.79-97.47, raloxifene), and 96.88 (96.49-97.24, tamoxifen). With the larger sample size, overall differences were statistically more marked ($p = 0.001$). Differences from placebo were most striking for tamoxifen ($p = 0.001$) and less so for hormone therapy ($p = 0.02$) and raloxifene ($p = 0.06$).

Mean adjusted 3MS scores over follow-up were also estimated for the subset of Caucasian women with baseline 3MS score < 95 , 1746 (28.1%) of the WHIMS participants and 86 (31.4%) of the CoSTAR participants. Because of the limited sample size, analyses were pooled across hysterectomy status,

FIG. 1. Cumulative distribution of baseline 3MS scores from the WHIMS and CoSTAR cohorts.

TABLE 2. AGE-ADJUSTED RELATIONSHIPS BETWEEN BASELINE DEMENTIA RISK FACTORS AND 3MS SCORES IN WHIMS AND CoSTAR

Baseline characteristic	WHIMS		CoSTAR		Consistency between trials <i>p</i> value ^a
	Mean 3MS (SE)	<i>p</i> value	Mean 3MS (SE)	<i>p</i> value	
Education					
<High school graduate	90.99 (0.17)	<0.001	91.85 (1.11)	0.0024	0.38
High school graduate	94.54 (0.10)		94.37 (0.45)		
Some college	95.38 (0.08)		94.49 (0.50)		
College graduate	96.58 (0.09)		95.94 (0.45)		
Ethnicity					
American Indian	94.18 (0.79)	<0.001	89.42 (2.44)	<0.001	0.18
Asian	92.61 (0.37)		89.31 (1.35)		
African American	90.80 (0.18)		91.27 (1.60)		
Hispanic/Latina	91.17 (0.31)		89.89 (4.22)		
White	95.78 (0.05)		95.20 (0.27)		
Other	92.98 (0.38)		94.21 (2.44)		
BMI, kg/m ²					
<24.9	95.45 (0.09)	<0.001	95.18 (0.50)	0.68	0.52
25.0–29.9	95.28 (0.08)		94.40 (0.44)		
30.0–34.9	95.13 (0.11)		94.69 (0.59)		
≥35.0	94.71 (0.14)		95.04 (0.74)		
Hypertension					
No	95.55 (0.07)	<0.001	95.01 (0.39)	0.44	0.70
Yes	94.92 (0.07)		94.60 (0.36)		
Diabetes					
No	95.31 (0.05)	<0.001	94.92 (0.28)	0.19	0.94
Yes	94.28 (0.18)		93.83 (0.78)		
Hysterectomy					
Yes	94.69 (0.08)	<0.001	94.89 (0.34)	0.66	0.046
No	95.56 (0.06)		94.64 (0.43)		

^aAnalyses of covariance.

which was included as an additional covariate. The adjusted mean postrandomization 3MS scores for women were 95.51 (95.33–95.68, placebo), 95.25 (95.07–95.43, hormone therapy), 94.46 (93.41–95.38, raloxifene), and 94.15 (93.04–95.12, tamoxifen). Overall differences among groups were significant ($p=0.003$), with the most marked differences between placebo and each of the active therapies. Figure 3 portrays the mean differences between each therapy and placebo for the women with baseline 3MS scores <95 and, for comparison, for all women. For each therapy, the relative decrements appeared to be larger for women with lower baseline 3MS scores: 0.26 (SE = 0.004) vs. 0.09 (0.001) for CEE therapy,

1.05 (0.41) vs. 0.32 (0.14) for raloxifene, and 1.36 (0.44) vs. 0.58 (0.16) for tamoxifen. For the separate tests of interaction between baseline 3MS and the relative effects of each drug vs. placebo, the p values were $p=0.03$ (CEE), $p=0.08$ (raloxifene), and $p=0.009$ (tamoxifen).

Discussion

Our findings add support to the hypothesis that tamoxifen, one of the most widely used selective estrogen receptor modulators (SERMs), may have a small negative effect on a global measure of cognitive function in older postmenopausal

TABLE 3. FITTED MEAN 3MS SCORES, BY TREATMENT ASSIGNMENT, WITH ADJUSTMENT FOR AGE, EDUCATION, DIABETES, HYPERTENSION, BMI, AND BASELINE 3MS (WHITES ONLY): STRATIFIED BY HYSTERECTOMY STATUS AND BASED ON LOG TRANSFORMATION OF (102 - 3MS SCORE): INCLUDED IN EACH CELL IS NUMBER OF WOMEN WHO HAD 3MS TESTING

Years since enrollment	WHIMS participants fitted mean (95% CI)		CoSTAR participants fitted mean (95% CI)	
	CEE therapy	Placebo	Raloxifene	Tamoxifen
No prior hysterectomy				
Year 1	97.26 (97.16–97.36) $n=1870$	97.34 (97.24–97.44) $n=1934$	96.90 (96.21–97.51) $n=51$	96.93 (96.19–97.58) $n=45$
Year 2	97.57 (97.47–97.66) $n=1801$	97.62 (97.52–97.71) $n=1852$	97.80 (97.11–98.39) $n=35$	96.75 (95.80–97.55) $n=30$
Year 3	97.60 (97.50–97.69) $n=1776$	97.74 (97.64–97.83) $n=1833$	97.07 (95.97–97.97) $n=18$	98.27 (97.35–99.01) $n=16$
Prior hysterectomy				
Year 1	96.89 (96.74–97.03) $n=1129$	97.04 (96.91–97.18) $n=1155$	96.80 (96.21–97.34) $n=75$	96.53 (95.88–97.11) $n=71$
Year 2	97.22 (97.08–97.35) $n=1053$	97.40 (97.27–97.53) $n=1093$	96.73 (95.99–97.38) $n=46$	96.46 (95.68–97.14) $n=47$
Year 3	97.41 (97.27–97.54) $n=1041$	97.43 (97.30–97.56) $n=1080$	96.83 (95.86–97.64) $n=25$	96.20 (95.01–97.18) $n=21$

FIG. 2. Mean deficits from 100 adjusted postrandomization 3MS scores across years 1–3 of follow-up. Estimates were limited to white participants and included age, baseline 3MS score, education, BMI, hypertension, and diabetes as covariates. Means are provided for women stratified by hysterectomy status and for all participants (with additional adjustment for hysterectomy status in the pooled analysis). Listed are *p* values from pairwise comparisons of each active therapy vs. the placebo from general linear models, which have not been adjusted for multiple testing.

women across 1–3 years. Raloxifene was also estimated to have a negative effect on cognition, which did not reach statistical significance. The primary conclusion from the full CoSTAR trial was that any effects that raloxifene and tamoxifen had on cognition over time were similar. The

magnitude of the mean differences, a 3MS point or less, may be undetectable and has little clinical significance for an individual woman. If, as seen in the WHIMS study,²⁷ these translate to an increased risk for cognitive impairment, they may have important public health consequences.

FIG. 3. Estimated mean relative decrements in postrandomization 3MS scores of active therapies compared with placebo therapy. Estimates are provided for all women and for the subset of women whose baseline 3MS score was <95.

Analogous to findings for CEE-based therapies, the estimated relative treatment effects on cognition for tamoxifen and raloxifene were larger among women whose baseline cognitive function was lower. For those with 3MS scores <95, estimated mean relative deficits exceeded twice their standard error, and formal tests of interactions were significant or of borderline significance. It would be of interest to examine whether relative deficits were larger at even lower 3MS scores; however, the relatively few CoSTAR women available in this range limit our ability to do this.

Our findings must be viewed with some caution. The covariate adjustment we used for cross-trial comparisons is not likely to provide as balanced comparisons as would be achieved within a randomized trial.²⁸ We cannot rule out that there may be some unmeasured factors that confound our comparisons. Nevertheless, this comparison is aided by the many commonalities between the trials, including similar aims, measures, training, and quality control procedures. Furthermore, the within-trial randomization reduces some of the biases compared with observational studies. CoSTAR was designed to promote comparisons with data collected by a substudy of WHIMS, the Women's Health Initiative Study of Cognitive Aging.²⁹ The analyses we describe, which were limited to women in both programs who had baseline assessments of cognition, were not described in study protocols and, thus, must be considered exploratory.

Clinical studies of raloxifene

Prior clinical studies examining the effect of raloxifene on cognition have been conducted in women with elevated risk for osteoporosis and have produced mixed results. The multiple outcomes of raloxifene evaluation (MORE) trial investigated the cognitive effects of 60 and 120 mg doses relative to placebo in 5386 women.^{4,5} After 3 years, the study found no effect of either dose on risk of Alzheimer's disease and a decreased risk of cognitive impairment with the 120-mg dose.⁵ Overall, there was no cognitive benefit of either dose on standardized tests of global cognitive function, memory, or other cognitive abilities, but analyses of a subgroup of women aged ≥ 70 years found some cognitive benefits of both raloxifene doses to memory and psychomotor speed.⁴ Nickelsen et al.⁴ conducted a 1-year randomized clinical trial in which 60 mg/day raloxifene was compared with placebo in 96 women (mean age 69 years) and found no significant differences in a battery of 11 cognitive tests. In the Eurolox 1 randomized trial of 1008 women, 60 mg raloxifene was associated with significantly worse reported memory/concentration over 6 months compared with 17 β -estradiol plus progestin therapy.³⁰ In a 3-month case-control study of the 60 mg dose in 49 women, raloxifene was associated with impaired attentional task performance but no difference in memory.³¹

Clinical studies of tamoxifen

Clinical trials of the effects of tamoxifen on cognitive function typically have been performed in combination with other chemotherapeutic agents and, thus, do not allow assessment of the effects of tamoxifen alone on cognitive function. Several small studies have suggested negative effects of tamoxifen on cognitive function, particularly memory. In a retrospective assessment by mail of 1163 women, Paganini-Hill and Clark¹⁰ found those who currently or in the past

received tamoxifen for breast cancer treatment reported seeing their doctors more often for memory concerns than never users. In another study, the cognitive function of 94 women receiving anastrozole, tamoxifen-alone, or both drugs for treatment of breast cancer was compared to that of 35 postmenopausal women without cancer who were chosen to have similar demographic backgrounds.³² Relative to controls, the patients receiving active therapy had poorer performance on tests of immediate verbal memory and processing speed. Although no patients in this trial received other chemotherapeutic agents, 67% of the women had received radiation therapy; thus, effects of this adjuvant therapy could not be excluded. Differences among active treatment groups were not explored. Other studies of small samples of breast cancer patients treated with chemotherapy and tamoxifen have confirmed the generally negative impact of tamoxifen on cognitive function beyond that attributable to adjuvant chemotherapy alone.³³

Potential mechanisms

The WHIMS program found that CEE-based hormone therapy increased the risks of dementia and produced a small average decrement in cognitive function.^{25,27} More recently, it has been reported that the adverse effects on cognition and increased risk for dementia of CEE-based therapy may be primarily conveyed through increased brain atrophy, including decreased hippocampal volume,^{34,35} and one report suggests that tamoxifen use also may be associated with smaller hippocampal volume.¹¹ However, raloxifene and tamoxifen may influence cognition through several pathways, which may be distinct from CEE-based therapy.³⁶ For example, raloxifene may alter brain activation patterns differently from estrogen therapy. Although in separate human studies, estrogen therapy and raloxifene treatments are associated with decreased left parahippocampal and increased right parietal lobe activation during visual recognition tasks; raloxifene, but not estrogen, was associated with increased activation in the right superior frontal gyrus and right precuneus.^{37,38}

Limitations

Our findings are limited by the relatively short follow-up period (primarily ≤ 2 years) and by the noted difficulties in comparisons between trials that do not contain a common arm. There likely are differences in selection factors in women who enrolled in WHI vs. those who enter a breast cancer prevention trial. Differences in eligibility criteria, recruitment practices, and retention may affect comparisons. Although the WHIMS and CoSTAR study periods overlapped, they were not identical, so that secular trends also may influence differences. Because eligibility was limited to women aged ≥ 65 years, our findings may not apply to younger women. The women in CoSTAR and WHIMS tend to be relatively healthy, and relatively few had chronic disease. Our findings are based on a test of global cognitive function and may not generalize to individual cognitive domains.

Conclusions

CEE, raloxifene, and tamoxifen all may induce small but detectable adverse effects on global cognition across 2–3 years

of therapy in women aged ≥ 65 years. These effects may be most pronounced among women with lower pretreatment levels of cognitive function.

Acknowledgments

This work was supported by the following sources. The Women's Health Initiative was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health, U.S. Department of Health and Human Services. WHIMS was funded by Wyeth Pharmaceuticals, Inc., St. Davids, PA, Wake Forest University Health Sciences, and by the National Heart, Lung, and Blood Institute (N01-WH-4-4221). STAR was supported by Public Health Service grants U10-CA-37377, U10-CA-69974, U10CA-12027, and U10CA-69651 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, AstraZeneca Pharmaceuticals, and Eli Lilly and Co. CoSTAR was funded by the National Institute on Aging (NO1-AG-2106). S.M.R. is supported by the Intramural Research Program, National Institute on Aging, and National Institutes of Health.

Disclosure Statement

The authors have no conflicts of interest to report.

References

1. Vogel VG, Constantino JP, Wickerham DL, et al. Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes. *JAMA* 2006;295:2727–2741.
2. Land SR, Wickerham DL, Constantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention. *JAMA* 2006;295:2741–2751.
3. Legault C, Maki P, Resnick S, et al. Effects of tamoxifen and raloxifene on memory and other cognitive abilities: Cognition in the Study of Tamoxifen and Raloxifene. *J Clin Oncol* 2009;40:5144–5152.
4. Nickelsen T, Lufkin EG, Riggs BL, Cox DA, Crook TH. Raloxifene hydrochloride, a selective estrogen receptor modulator: Safety assessment of effects on cognitive function and mood in postmenopausal women. *Psychoendocrinology* 1999;24:115–128.
5. Yaffe K, Krueger K, Sarkar S, et al. Cognitive function in postmenopausal women treated with raloxifene. *N Engl J Med* 2001;344:1207–1213.
6. Yaffe K, Krueger K, Cummings SR, et al. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: The Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. *Am J Psychiatry* 2005;162:683–690.
7. Wong M, Moss R. Electrophysiological evidence for a rapid membrane action of the gonadal steroid, 17 beta-estradiol, on CA1 pyramidal neurons of the rat hippocampus. *Brain Res* 1991;543:148–152.
8. Murphy D, Segal M. Regulation of dendritic spine density in cultured rat hippocampal neurons by steroid hormones. *J Neurosci* 1996;16:4059–4068.
9. Simpkins JW, Green PS, Gridely KE, Singh M, de Fiebre NC, Rajakumar G. Role of estrogen replacement therapy in memory enhancement and the prevention of neuronal loss associated with Alzheimer's disease. *Am J Med* 1997;103:19S–25S.
10. Paganini-Hill A, Clark LJ. Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. *Breast Cancer Res Treat* 2000;64:165–176.
11. Eberling JL, Wu C, Tong-Turnbeaugh R, Jagust WJ. Estrogen- and tamoxifen-induced effects on brain structure and function. *Neuroimage* 2004;21:364–371.
12. Silva I, Mello LE, Freymuller E, Haidar MA, Baracat EC. Estrogen, progestogen, and tamoxifen increase synaptic density of the hippocampus of ovariectomized rats. *Neurosci Lett* 2000;291:183–186.
13. Breuer B, Anderson R. The relationship of tamoxifen with dementia, depression, and dependence in activities of daily living in elderly nursing home residents. *Women Health* 2000;31:71–75.
14. Dhandapani KM, Wade FM, Mahesh VB, Brann DW. Astrocyte-derived transforming growth factor- β mediates the neuroprotective effects of 17 β -estradiol: Involvement of nonclassical genomic signaling pathways. *Endocrinology* 2005;146:2749–2759.
15. Ernst T, Chang L, Cooray D, et al. The effects of tamoxifen and estrogen on brain metabolism in elderly women. *J Natl Cancer Inst* 2002;94:592–597.
16. The Women's Health Initiative Study Group Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 1998;19:61–109.
17. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): A trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Control Clin Trials* 1998;19:604–621.
18. Teng EL, Chui HC. The Modified Mini Mental State (3MS) Examination. *J Clin Psychiatry* 1987;48:314–318.
19. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879–1886.
20. Bravo G, Hebert R. Reliability of the Modified Mini-Mental State Examination in the context of a two-phase community prevalence study. *Neuroepidemiology* 1997;16:141–148.
21. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–333.
22. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogens in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–1712.
23. Rapp SR, Espeland MA, Hogan P, Jones BN, Dugan E. Baseline experience with the Modified Mini-Mental State Exam: The Women's Health Initiative Memory Study (WHIMS). *Aging Mental Health* 2003;7:217–223.
24. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS system for mixed models. Cary, NC: SAS Institute, 1996.
25. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women. *JAMA* 2004;291:2959–2968.
26. Espeland MA, Rapp SR, Robertson J, et al. Benchmarks for designing two-stage studies using Modified Mini-Mental State Examinations: Experience from the Women's Health Initiative Memory Study. *Clin Trials* 2006;3:99–106.

27. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogen alone, pooled hormone therapy, and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Results from the Women's Health Initiative Memory Study. *JAMA* 2004;291:2947-2958.
28. Lumley T. Network meta-analysis for indirect treatment comparisons. *Statist Med* 2002;21:2323-2324.
29. Resnick SM, Coker LH, Maki PM, Rapp SR, Espeland MA, Shumaker SA. The Women's Health Initiative Study of Cognitive Aging (WHISCA): A randomized clinical trial of the effects of hormone therapy on age-associated cognitive decline. *Clin Trials* 2004;1:440-450.
30. Neven P, Quail D, Marin F, et al. Comparing raloxifene with continuous combined estrogen-progestin therapy in postmenopausal women: Review of Euralox 1. *Maturitas* 2005; 52:87-101.
31. Natale V, Albertazzi P, Missiroli N, Pedrini D, Salgarello M. Effects of raloxifene on mood, sleep, libido and cognitive function in postmenopausal healthy women: A pilot study. *Maturitas* 2004;48:59-63.
32. Jenkins V, Shilling V, Fallowfield L, Howell A, Hutton S. Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. *Psychooncology* 2004;13:61-66.
33. Bender C, Sereika S, Berga SM, Vogel C, Brufsky AM, Ryan CM. Cognitive impairment associated with adjuvant therapy in women with breast cancer. *Psychooncology* 2006;15: 422-430.
34. Coker LH, Hogan PE, Bryan NR, et al. The effects of postmenopausal hormone therapy on volumetric sub-clinical cerebrovascular disease: The Women's Health Initiative Memory Study Magnetic Resonance Imaging Study (WHIMS-MRI). *Neurology* 2009;72:125-134.
35. Resnick SR, Espeland MA, Jaramillo SA, et al. Effects of postmenopausal hormone therapy on regional brain volumes in older women: The Women's Health Initiative Magnetic Resonance Imaging Study (WHIMS-MRI). *Neurology* 2009;72:135-142.
36. Ciriza I, Carrero P, Azcoitia I, Lundeen SG, Garcia-Segura LM. Selective estrogen receptor modulators protect hippocampal neurons from kainic acid excitotoxicity: Differences with the effect of estradiol. *Int J Neurobiol* 2004;61: 209-221.
37. Neele SJ, Rombouts SA, Bierlaagh ME, Barkhof F, Scheltens P, Netelenbos JC. Raloxifene affects brain activation patterns in postmenopausal women during visual encoding. *J Clin Endocrinol Metab* 2001;86:1422-1424.
38. Resnick SM, Maki PM, Golski S, Kraut MA, Zonderman AB. Effects of estrogen replacement therapy on PET cerebral blood flow and neuropsychological performance. *Horm Behav* 1998;34:171-182.

Address correspondence to:

Mark A. Espeland, Ph.D.

Department of Biostatistical Sciences

Wake Forest University School of Medicine

Medical Center Boulevard

Winston-Salem, NC 27157

E-mail: mespelan@wfubmc.edu