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ORIGINAL REPORT

Meta-Analysis of Cognitive Functioning in Breast Cancer Survivors Previously Treated With Standard-Dose Chemotherapy

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See accompanying editorial on page 3568; listen to podcast by Drs Dhillon and Vardy at www.jco.org/podcasts

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ABSTRACT

Purpose
Evidence is mixed regarding long-term cognitive deficits in patients treated with chemotherapy. Previous meta-analyses have not focused specifically on the postchemotherapy period and have not incorporated several recent studies. The goal of the current study was to conduct a meta-analysis of cognitive functioning in breast cancer survivors who were treated with chemotherapy ≥ 6 months previously.

Methods
A search of PubMed, PsycInfo, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Library yielded 2,751 abstracts, which were independently evaluated by pairs of raters. Meta-analysis was conducted on 17 studies of 807 patients previously treated with standard-dose chemotherapy for breast cancer. Neuropsychological tests were categorized according to eight cognitive domains: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability.

Results
Deficits in cognitive functioning were observed in patients treated with chemotherapy relative to controls or prechemotherapy baseline in the domains of verbal ability ($g = -0.19$; $P < .01$) and visuospatial ability ($g = -0.27$; $P < .01$). Patients treated with chemotherapy performed worse than noncancer controls in verbal ability and worse than patients treated without chemotherapy in visuospatial ability (both $P < .01$). Age, education, time since treatment, and endocrine therapy did not moderate observed cognitive deficits in verbal ability or visuospatial ability (all $P \geq .51$).

Conclusion
Results indicate that, on average, observed cognitive deficits in patients with breast cancer previously treated with chemotherapy are small in magnitude and limited to the domains of verbal ability and visuospatial ability. This information can be used to inform interventions to educate patients with breast cancer regarding the long-term impact of chemotherapy on cognitive functioning.

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INTRODUCTION

Anecdotal reports of "chemo brain," or a loss of mental acuity associated with chemotherapy, are well-publicized[1,2] and are a source of significant concern among patients with cancer treated with chemotherapy.[3] Data suggest that patients' concerns are merited; cognitive deficits are pronounced during treatment. Cross-sectional data indicate that rates of moderate or severe impairment ranging from 16% to 75% in patients with breast cancer during chemotherapy as compared with 4% to 11% in healthy controls.[4-6] Data are conflicting, however, regarding the persistence of cognitive deficits after treatment. Several studies have detected cognitive deficits in breast cancer survivors previously treated with chemotherapy,[7-9] whereas other studies have not.[10-13] In addition to possible persistent effects, recent data suggest the possible development of late cognitive effects not present at the end of treatment.[7] Meta-analysis, in which a weighted average of effect sizes is calculated across individual studies, is an ideal technique to help reconcile these conflicting data. Pooling across studies increases power to find

effects where they exist, which is particularly important in cancer survivors, as data suggest that cognitive deficits are subtle in nature.[6] Consequently, the goal of the current study was to conduct a meta-analysis examining cognitive functioning in cancer survivors previously treated with chemotherapy. The meta-analysis focuses on women with breast cancer, as the vast majority of existing research has been conducted in this population.

Although four previous meta-analyses have examined cognitive functioning in patients treated with chemotherapy, none has focused exclusively on the post-treatment period. Anderson-Hanley et al[14] used meta-analysis to examine neuropsychological effects of cancer treatment, including chemotherapy, interferon alfa, interleukin-2, radiotherapy, total-brain irradiation, hematopoietic cell transplant, and biologic therapy. Patients were assessed during treatment or shortly thereafter in 13 of 30 included studies, whereas eight of 30 studies included patients with breast cancer. Comparing patients with population norms, statistically significant medium to large effect sizes ($d = -0.48$ to -0.93) were found in the domains of verbal memory, executive function, and motor skill. Comparing patients with controls, statistically significant small to medium effect sizes ($d = -0.24$ to -0.70) were found across all domains. Patients performed worse in all comparisons. Significant effects were not present when comparing patients to their own baseline. This study suggests that treatment for cancer is associated with cognitive deficits in patients compared with population norms and controls. However, the effects of chemotherapy specifically were unclear as a result of the wide variety of treatments examined.

Jansen et al[15] conducted a meta-analysis to examine neuropsychological effects of chemotherapy on patients with cancer. Included were 16 studies, nine of which included patients with breast cancer, and the majority assessed cognition during treatment or shortly thereafter. When patients were compared with normative data, statistically significant medium effect sizes ($d = -0.52$ to -0.78) were found in the domains of executive function, information processing speed, verbal memory, and visual memory. Patients treated with chemotherapy performed worse in all domains. When patients were compared with healthy controls, small, statistically significant effect sizes were found in language and verbal memory, with patients performing worse. When patients treated with chemotherapy were compared with control patients treated with local therapy or with their own baseline scores, no significant differences were observed. This analysis suggests that deficits associated with chemotherapy are small to moderate and may depend on the study methodology used.

Two meta-analyses[16,17] have examined the neuropsychological effects of chemotherapy specifically on women diagnosed with breast cancer. Both analyses included studies that examined patients currently undergoing treatment as well as those who had completed treatment months or years previously. Falleti et al[16] included data from five cross-sectional studies and one prospective study. Analysis of the five cross-sectional studies revealed that the chemotherapy group performed worse than controls in all comparisons. Of these, the largest differences were observed in the domains of motor function ($d = -0.51$), spatial ability ($d = -0.48$), and language ($d = -0.41$). The authors also reported statistically significant associations between larger effect sizes and shorter time since last chemotherapy, larger percentage of patients treated with tamoxifen, and younger patient age. These findings suggest that subsets of patients with breast cancer may be particularly vulnerable to the cognitive effects of chemotherapy.

A similar meta-analysis was conducted by Stewart et al,[17] who analyzed seven studies in which patients with breast cancer were compared with baseline data or controls, including the six examined by Falleti.[16] Of eight cognitive domains evaluated, statistically significant small to medium weighted pooled effect sizes ($d = -0.22$ to -0.37) were found in seven: working memory, short-term memory, long-term memory, speed of processing, language, spatial abilities, and motor abilities. Patients treated with chemotherapy fared worse in all domains. The largest differences were observed in language ($d = -0.37$) and short-term memory ($d = -0.31$). However, the fail-safe number was lower than recommended, suggesting that results may not be replicable with more studies. Thus additional studies yielding similar results would increase confidence in these findings.

Taken together, existing meta-analyses suggest that chemotherapy administration confers a risk of cognitive deficits. Although the cognitive consequences of chemotherapy is an active area of research, the most recent meta-analysis was published in 2006. Thus existing meta-analytic studies do not incorporate recent findings. In addition, none specifically examined the presence and magnitude of cognitive deficits in the post-treatment period. If cognitive deficits occur during treatment but resolve thereafter, then studies including patients primarily receiving treatment may negatively influence findings to give the appearance of cognitive deficits in all survivors. However, it is possible that deficits occurring during treatment may persist in the months and years that follow. Whether this is the case cannot be determined from existing meta-analyses.

The objective of the current meta-analysis was to examine literature regarding cognitive deficits in patients with breast cancer in the postchemotherapy period. Toward this end, we sought to identify all neuropsychological studies of women with breast cancer who were treated with standard-dose chemotherapy at least 6 months previously. Comparisons with noncancer controls, patients with breast cancer treated without chemotherapy, and patients' own prechemotherapy baseline were selected. A secondary objective was to examine sociodemographic and clinical moderators of cognitive function in patients with breast cancer, including age, education, time since chemotherapy, and treatment with endocrine therapy.

METHODS

Search Strategy

The study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18] Identification of appropriate studies began with searches of the electronic databases PubMed, PsycInfo, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane library. The search terms used for PubMed were the following: (1) cognitive effects AND cancer patients AND chemotherapy, (2) cognition AND cancer AND chemotherapy, (3) cognition disorders/chemically induced AND cancer AND chemotherapy, (4) [cognition disorders/chemically induced OR cognition disorders] AND [neoplasms/drug therapy OR neoplasms/radiotherapy OR neoplasms], (5) [cognition disorders or cognition or cognitive effects and cancer] AND chemotherapy, (6) chemobrain AND cancer, and (7) cognitive impairment AND breast cancer. The search terms used for PsycInfo, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane library were as follows: (1) cognitive disorders AND chemotherapy AND cancer, (2) cognition AND chemotherapy AND cancer, (3) chemobrain OR chemobrain OR chemo-brain, and (4) cognitive effects and

chemotherapy and cancer. Searches were limited to studies published in the English language. Reference lists from publications retrieved and from relevant systematic reviews and meta-analyses were also examined to identify studies.[14-17] The search was inclusive of studies published between 1937 and June 2011.

Selection Strategy

Selection of abstracts for full review was conducted by four pairs of raters. Each person reviewed the abstracts independently and generated a list of studies to retrieve for full-text review. Lists were then compared and discrepancies resolved by consensus. Four inclusion criteria were applied to studies retrieved. First, each study must have reported objective neuropsychological data on women with breast cancer. Studies reporting data from screening measures only (eg, Mini Mental Status Exam, High Sensitivity Cognitive Screen, Blessed Information-Memory-Concentration test) were excluded. Second, the chemotherapy sample in each study must have consisted entirely of patients who had completed standard-dose chemotherapy at least 6 months previously. Six months postchemotherapy was selected as a cutoff point to exclude assessment of the acute effects of chemotherapy. Studies known to include patients with disease recurrence were excluded. Third, the results reported must have included statistical significance testing of differences between a chemotherapy sample and a comparison group of individuals without cancer, patients with cancer treated without chemotherapy (eg, radiation, surgery), or patients' own prechemotherapy baseline. Studies of patients treated with biologic response modifiers, cranial irradiation, or total-body irradiation were excluded. Fourth, each study must have reported original data. Reviews, commentaries, case reports, and meta-analyses were excluded. Studies selected for full-text review were examined independently by pairs of raters. Data were independently extracted and checked by rater pairs. Discrepancies in study selection and data extraction were resolved by consensus. Data extracted included neuropsychological test data (ie, means scores, standard deviations, sample size), study design characteristics (ie, type of control group, timing of assessments), and chemotherapy patient characteristics (ie, age, education, time since chemotherapy, endocrine therapy and radiation). When published articles did not present sufficient data to calculate effect sizes, authors were contacted for the required information.

Statistical Analysis

Meta-analytic procedures were based on those outlined by Hedges and Olkin.[19] From the results reported or provided on request by one of the publication authors, an effect size estimate (g) was first calculated to indicate the difference between the chemotherapy and control group divided by the pooled standard deviation. Individual effect size estimates were computed for each reported neuropsychological test. The information used to generate g values was based on between-subjects differences at the final measurement point for the chemotherapy and control groups or within-subjects change from prechemotherapy baseline to the last measurement point in longitudinal designs. Random effects models were used to calculate effect sizes. Random effects models assume that analyzed studies represent a random sample of effect sizes, which facilitates the generalizability of results.[20]

In addition to describing the differences between the chemotherapy and control groups, we examined several moderating characteristics that could potentially influence the magnitude of the observed group differences. Moderating characteristics were identified a priori. Specifically, studies were stratified by design (ie, longitudinal, chemotherapy *v* local therapy, and chemotherapy *v* no cancer). In addition, age, education, mean time since completion of chemotherapy, and percentage of the sample treated with endocrine therapy were examined as continuous moderators using meta-regression with method of moments estimation.[21] Because recent data suggest that tamoxifen may exert a greater effect on cognitive functioning than aromatase inhibitors,[22] we also examined the moderating effects of the percentage of the sample treated with tamoxifen.

Overall effects for each cognitive domain were assessed for degree of publication bias, or overrepresentation of positive effects, using funnel plots and trim and fill. Funnel plots display the relationship between each study's effect size and SE; an asymmetric distribution of studies around the mean effect size indicates the possibility of publication bias.[20] Trim and fill iteratively removes extreme small studies until the funnel plot is symmetric, thus providing an unbiased estimate of effect size. Removed studies are then added back, as well as a mirror image of each, to correct for the diminished variance resulting from study removal.[23,24] To determine whether the observed overall effect is robust, Orwin's failsafe N was used.[25] A trivial effect was set a priori to $g = -0.10$, and the mean point estimate in missing studies was conservatively assumed to be -0.005. The number of studies is represented by k, in contrast to the number of participants in each study (N). Analyses were conducted using Comprehensive Meta Analysis software.[21]

RESULTS

Study Selection

A total of 2,751 abstracts were identified through electronic databases (see Fig 1). Of these, 160 were duplicates, resulting in 2,591 unique abstracts. Full text was retrieved for 36 studies.[7-13,26-54] On review of these studies, 16 were eliminated because they did not meet inclusion criteria for the meta-analysis. One additional study was identified through a hand search of reference lists.[55] Of the 21 studies that met all inclusion criteria,[7-12,28,29,31,36,37,42,43,45,46,48,50,52-55] sufficient data were not available to compute an effect size for four studies.[8,31,42,53] Consequently, 17 studies were included in the meta-analysis.[7,9-12,28,29,36,37,43,45,46,48,50,52,54,55] Of included studies, four were longitudinal comparisons of patients who received chemotherapy,[7,28,50,54] six compared patients who received chemotherapy with patients with cancer who received local therapy (ie, radiation, surgery) or endocrine therapy,[10,36,37,43,46,55] three compared patients who received chemotherapy with individuals without cancer,[9,45,52] two included two types of comparisons (ie, longitudinal, chemotherapy *v* local or endocrine therapy only),[12,48] and two included all three types of comparisons (ie, longitudinal, chemotherapy *v* local or endocrine therapy only, chemotherapy *v* no cancer).[11,29] Study characteristics are displayed in Table 1.

Measured Outcomes

To ease interpretability of results, individual neuropsychological tests were categorized according to the predominant cognitive domain they assessed.[56] The eight domains were attention (ie, the ability to focus on incoming stimuli), executive functioning (ie, the ability to plan, initiate, and carry out goal-directed behavior as well as monitor performance), information processing (ie, the ability to sustain attention, engage in visual scanning, and activate and inhibit rapid responses), motor speed (ie, manual dexterity), verbal ability (ie, word finding, vocabulary, and speed and ease of word generation), verbal memory (ie, immediate and delayed recall as well as recognition of word lists), visual memory (ie, immediate and delayed recall as well as recognition of visual information), and visuospatial ability (ie, ability to copy a complex two-dimensional figure and reconstruct complex two-dimensional patterns).[56] Neuropsychological tests and their corresponding cognitive domains are displayed in Appendix Table A1 (online only).

Description of Study Participants

Included studies comprised a sample of 807 patients who received chemotherapy, 391 patients who received local or endocrine therapy, and 291 individuals without cancer. The mean age of the chemotherapy sample was 52.3 years. Of studies reporting education

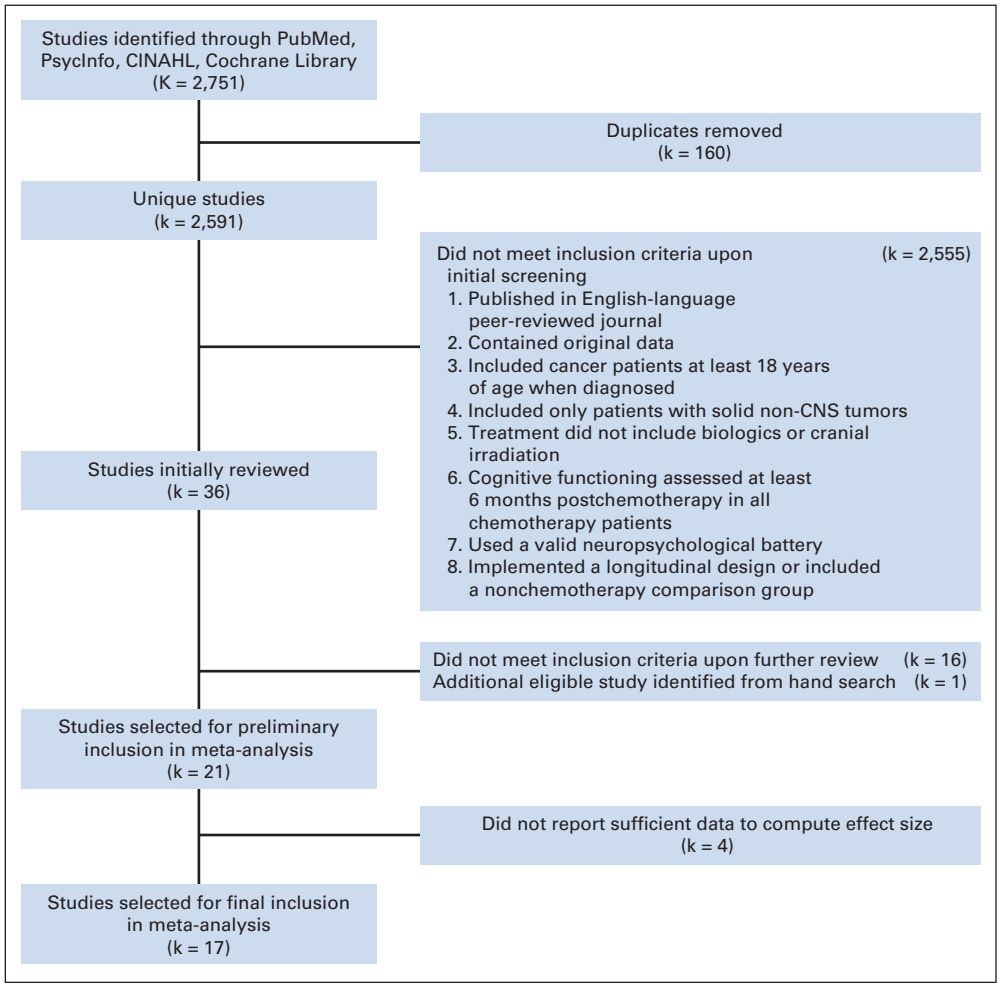

Fig 1. Selection of included studies. CINAHL, Cumulative Index to Nursing and Allied Health Literature.

as a continuous outcome (k = 11), the mean years of education was 13.9. The mean time since completion of chemotherapy treatment was 2.9 years (k = 17). Of studies reporting the number of chemotherapy patients receiving concurrent radiation (k = 10), 61% of patients received radiation. In studies of patients with breast cancer reporting treatment with endocrine therapy (k = 15), 55% of patients received endocrine therapy (ie, tamoxifen or aromatase inhibitors). In studies reporting the type of endocrine therapy (k = 11), 49% of all patients received tamoxifen.

Meta-Analysis

Weighted average effect sizes for each cognitive domain are shown in Table 2. Patients treated with chemotherapy displayed significantly worse cognitive functioning in the domains of verbal ability and visuospatial ability (both $P < .01$); forest plots are displayed in Figures 2 and 3, respectively. Moderator analyses were conducted for verbal ability and visuospatial ability. Regarding verbal ability, study design was a significant moderator such that patients treated with chemotherapy performed significantly worse than noncancer controls ($g = -0.21$; $P < .01$), but not compared with their own prechemotherapy baseline or patients treated without chemotherapy (both $P \geq .14$; Fig 2). Meta regression indicated that patient age was not a significant moderator of verbal ability (k = 12; $B = 0.008$; $P = .61$), nor was time since chemotherapy (k = 12; $B = 0.009$; $P = .69$), education (k = 6; $B = 0.002$; $P = 1.00$), or endocrine therapy (k = 10; $B = 0.078$; $P = .88$). When endocrine therapy analyses were restricted to the percentage of the sample treated with tamoxifen (ie, not aromatase inhibitors), results remained nonsignificant (k = 7; $B = 0.031$; $P = .95$). Regarding visuospatial ability, study design was a significant moderator such that patients treated with chemotherapy performed significantly worse than patients treated without chemotherapy ($P < .01$). However, there were no differences when comparing patients treated with chemotherapy with their own baseline or noncancer controls (both $P \geq .86$; Fig 3). Meta regression indicated that patient age (k = 8; $B = 0.004$; $P = .78$), time since chemotherapy (k = 8; $B = 0.002$; $P = .94$), education (k = 5; $B = 0.445$; $P = .60$), and endocrine therapy (k = 6; $B = -0.020$; $P = .96$) did not moderate visuospatial ability. Restriction of endocrine therapy analyses to percentage of the sample treated with tamoxifen also yielded nonsignificant results (k = 4; $B = -0.055$; $P = .89$).

Regarding publication bias, the funnel plot for verbal ability showed a greater number of studies to the right of the mean, whereas trim and fill imputed five studies (Fig 4A). The adjusted effect size after the trim and fill procedure was $g = -.19$ (95% CI, −0.31 to −0.08), which was the same as the unadjusted estimate of *g*. This suggests that systematic bias does not significantly contribute to our estimate of the effect of chemotherapy on verbal ability. Regarding the robustness of the observed difference in verbal ability between patients treated with

Table 1. Characteristics of Included Studies (k = 17)

	Sample										
First Author (year)	Chemo (n)	Type of Controls (1)	Control n (1)	Type of Controls (2)	Control n (2)	Concurrent Radiation in Chemo Group (%)	Endocrine Treatment in Chemo Group (%)	Average Chemo Patient Age (years)	Average Chemo Patient Education (years)	Methods: Assessments Included in Meta-Analysis	Outcomes: Domains Assessed
Ahles (2002)[46]	35	Local therapy	35			0	38 tamoxifen, 0 AIs	59.1	14	1 time: mean of 9.4 years post chemo	Attention, executive function, motor speed, verbal ability, verbal memory, visual memory, visuospatial ability
Bender (2006)[48]	34	Local therapy	5			Not stated	33 tamoxifen, 0 AIs	41.9	14.4	Prechemo, 1 year post chemo	Verbal memory, visual memory
Collins (2009)[12]	53	Endocrine therapy only	40			Not stated	34 tamoxifen, 30 AIs, 8 both	57.9	14.6	Prechemo, 1 year later	Attention, executive function, information processing, motor speed, verbal memory, visual memory, verbal ability, visuospatial ability
Donovan (2005)[10]	60	Radiation only	83			100	51.70 tamoxifen or AIs	52.3	15	1 time: 6 months post chemo	Attention, executive function, motor speed, verbal ability, verbal memory, visual memory
Hurria (2006)[54]	28	None	0			Not stated	89% tamoxifen or AIs	71	86% more than 12 years	Prechemo, 6 months post chemo	Attention, executive function, verbal ability, verbal memory, visual memory, visuospatial ability
Inagaki (2007)[52]	73	Women without cancer	55	Local therapy not included due to overlap with Yoskikawa et al (2005)		32	29 tamoxifen or AIs	48.2	12.8	1 time: 3.25 years post surgery	Attention, verbal memory, visual memory
Jansen (2010)[28]	71	None	0			Not stated	61 tamoxifen or AIs	50.3	15.7	Prechemo, 6 months post chemo	Attention, executive function, motor speed, verbal ability, verbal memory, visuospatial ability
Jenkins (2006)[29]	85	Local or endocrine therapy	43	Women without cancer	49	84	54 tamoxifen, 16 AIs	51.5	12	Prechemo, 1 year post chemo	Attention, executive function, information processing, verbal memory, visual memory
Jim (2009)[9]	97	Women without cancer	97			86	Not stated	50	48% some college or less	1 time: 6 months post chemo	Attention, executive function, information processing, verbal ability, verbal memory, visual memory

(continued on following page)

Table 1. Characteristics of Included Studies (k = 17)

	Sample										
First Author (year)	Chemo (n)	Type of Controls (1)	Control n (1)	Type of Controls (2)	Control n (2)	Concurrent Radiation in Chemo Group (%)	Endocrine Treatment in Chemo Group (%)	Average Chemo Patient Age (years)	Average Chemo Patient Education (years)	Methods: Assessments Included in Meta-Analysis	Outcomes: Domains Assessed
Schagen (1999)[36]	39	Local therapy	34			Not stated	51 tamoxifen	47.1	49% completed university or graduate school	1 time: mean of 1.9 years post chemo	Attention, executive function, information processing, motor speed, verbal ability, verbal memory, visual memory, visuospatial ability
Scherwath (2006)[37]	23	Local therapy	29			Not stated	44 tamoxifen	51.8	34.8% college graduate	1 time: mean of 5.2 years post chemo	Attention, executive function, verbal ability, verbal memory, visual memory
Schagen (2006)[11]	39	Local therapy	57	Women without cancer	60	100	100 tamoxifen	45.5	Not stated	Prechemo, 6 months post chemo	Attention, executive function, information processing, motor speed, verbal ability, verbal memory, visual memory
van Dam (1998)[43]	36	Local therapy	34			100	100 tamoxifen	48.1	44% completed university or graduate school	1 time: 1.9 years post chemo	Attention, executive function, verbal ability, verbal memory, visual memory, visuospatial ability
Wefel (2010)[7]	42	None	0			57	10 tamoxifen	48.8	13	Prechemo, 1.1 years later	Attention, executive function, verbal ability, verbal memory
Wefel (2004)[50]	18	None	0			33	0	45.4	14	Prechemo, 1 year post chemo	Attention, executive function, motor speed, verbal ability, verbal memory, visual memory, visuospatial ability
Yamada (2010)[45]	30	Women without cancer	30			Not stated	Not stated	72.8	14.4	1 time: mean of 16.8 years post chemo	Attention, executive function, verbal ability, verbal memory, visual memory, visuospatial ability
Yoshikawa (2005)[55]	44	Local therapy	31			16	70.1 tamoxifen	48.3	12.6	1 time: mean of 3.5 years post chemo	Attention, verbal memory, visual memory

Abbreviations: AIs, aromatase inhibitors; chemo, chemotherapy.

chemotherapy and controls, Orwin's failsafe N indicated that 14 nonsignificant studies would be needed to render group differences trivial. For visuospatial ability, the funnel plot showed a greater number of studies to the right of the mean, whereas trim and fill imputed three studies (Fig 4B). The adjusted effect size after the trim and fill procedure was $g = -0.28$ (95% CI, -0.46 to -0.09), suggesting a slightly larger difference between patients treated with chemotherapy and controls than the unadjusted estimate of g but within the CI of the unadjusted g. Regarding the robustness of the observed difference in visuospatial ability between patients treated with chemotherapy and controls, Orwin's failsafe N indicated that 16 nonsignificant studies would be needed to render group differences trivial.

DISCUSSION

The current meta-analysis synthesized data from 17 studies examining the post-treatment effects of chemotherapy on cognitive functioning

Table 2. Weighted Average Effect Sizes By Cognitive Domain

Domain	k	No. of Comparisons	Effect Size (*g*)	95% CI	*P*
Attention	16	21	−0.02	−0.12 to 0.08	.743
Executive functioning	14	19	−0.12	−0.23 to 0.00	.052
Information processing	6	11	−0.11	−0.25 to 0.03	.122
Motor speed	8	11	0.06	−0.37 to 0.49	.785
Verbal ability	12	15	−0.19	−0.30 to −0.07	.002
Verbal memory	17	23	−0.06	−0.18 to 0.06	.313
Visual memory	15	21	0.02	−0.09 to 0.13	.730
Visuospatial ability	8	9	−0.27	−0.45 to −0.08	.006

in patients with breast cancer. Results indicated that patients previously treated with chemotherapy performed significantly worse on tests of verbal ability than individuals without cancer. In addition, patients treated with chemotherapy performed significantly worse on tests of visuospatial ability than patients treated without chemotherapy. There was also a nonsignificant trend toward worse performance in executive functioning for patients treated with chemotherapy. The magnitude of all effect sizes was small. There were no differences in cognitive performance on tests of attention, information processing, motor speed, verbal memory, or visual memory. Consequently, the current study suggests that ≥ 6 months after chemotherapy, patients with breast cancer can expect slight, focused cognitive deficits in verbal and visuospatial ability and normal functioning in other cognitive domains, on average.

These findings provide a marked contrast to the larger and more pervasive deficits reported by previous meta-analyses,[14-17] suggesting that cognitive deficits after chemotherapy for breast cancer are relatively mild compared with other types of cancer treatment and with the active treatment period. All four of the previous meta-analyses reported significant impairments in multiple domains of functioning, most frequently motor function,[14,16,17] memory,[14,15] executive functioning,[14,15] verbal ability,[16,17] and visuospatial ability.[16,17] In contrast, our meta-analysis found deficits only in verbal ability and visuospatial ability. The degree of overlap in studies between this meta-analysis and the previous ones was small; the largest number of common studies was four.[15,17] Thus, taken together with previous meta-analyses, our findings regarding deficits in verbal ability and visuospatial ability seem to be robust.

The only moderator of our findings was study design. Patients treated with chemotherapy performed worse than individuals without cancer on tests of verbal ability and worse than patients treated without chemotherapy on tests of visuospatial ability. Patients showed no differences in postchemotherapy verbal ability and visuospatial ability compared with their own prechemotherapy baseline. Although it seems counterintuitive that patients treated with chemotherapy would show visuospatial deficits relative to other patients with cancer but not individuals without cancer, for this cognitive domain there was only one comparison between patients treated with chemotherapy and individuals without cancer. As a result, it is unknown how this nonsignificant difference would change with a larger number of comparisons. Our findings regarding the moderating influence of study design are congruent with previous meta-analyses suggesting that the largest cognitive differences are observed between patients and noncancer controls, whereas within-patient longitudinal comparisons tend to yield smaller and nonsignificant results.[14,15] It is currently unclear whether the pattern of results reflects systematic bias in recruiting noncancer controls with higher-than-average cognitive functioning, an effect of cancer on cognitive functioning, or the presence of confounding variables that differ in patients between pre- and postchemotherapy cognitive assessments (eg, depression, anxiety). Alternately, worsening cognitive functioning may be offset by the practice effects of longitudinal testing, resulting in nonsignificant within-person change over time.[57]

Neither age, education, time since chemotherapy, or endocrine therapy was a significant moderator of verbal ability or visuospatial ability. These findings are surprising in light of the fact that age and

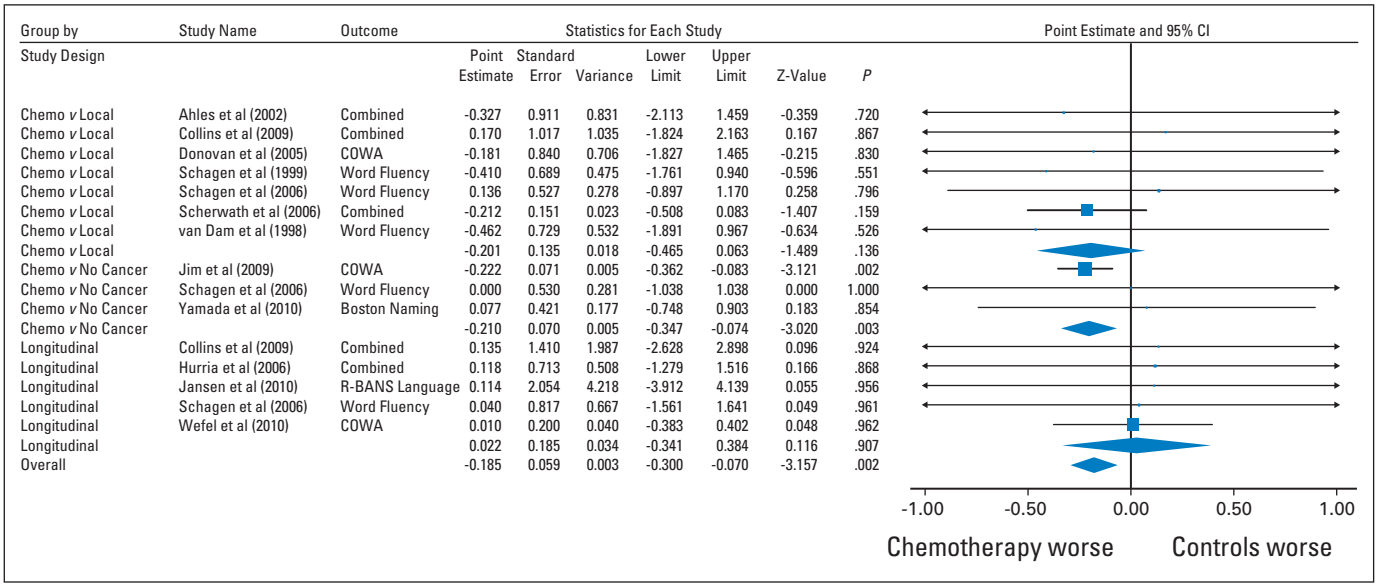

Fig 2. Forest plot of effect sizes (*g*) for studies assessing verbal ability. Chemo, chemotherapy; COWA, Controlled Oral Word Association; R-BANS, Repeatable Battery of Adult Neuropsychological Status.

Group by Study Design	Study Name	Outcome	Point Estimate	Standard Error	Variance	Lower Limit	Upper Limit	Z-Value	P
Chemo *v* Local	Ahles et al (2002)	Block Design	-0.461	0.313	0.098	-1.075	0.153	-1.472	.141
Chemo *v* Local	Collins et al (2002)	WAIS-III Block Design	0.182	1.154	1.332	-2.080	2.444	0.157	.875
Chemo *v* Local	Schagen et al (1999)	Complex Figure Copy	-0.236	0.150	0.022	-0.530	0.057	-1.580	.114
Chemo *v* Local	van Dam et al (1998)	Complex Figure Copy	-0.317	0.152	0.023	-0.615	-0.019	-2.082	.037
Chemo *v* Local			-0.291	0.101	0.010	-0.489	-0.094	-2.898	.004
Chemo *v* No Cancer	Yamada et al (2010)	Combined	-0.028	0.429	0.184	-0.869	0.813	-0.064	.949
Chemo *v* No Cancer			-0.028	0.429	0.184	-0.869	0.813	-0.064	.949
Longitudinal	Collins et al (2009)	WAIS-III Block Design	0.089	1.553	2.413	-2.955	3.134	0.057	.954
Longitudinal	Hurria et al (2006)	Combined	-0.045	0.739	0.546	-1.493	1.403	-0.061	.952
Longitudinal	Jansen et al (2010)	R-BANS Visuospatial Skill	-0.426	1.992	3.967	-4.330	3.478	-0.214	.830
Longitudinal	Wefel et al (2004)	Block Design	0.385	0.881	0.777	-1.342	2.112	0.437	.662
Longitudinal			0.091	0.514	0.264	-0.917	1.098	0.176	.860
Overall			-0.265	0.096	0.009	-0.453	-0.076	-2.753	.006

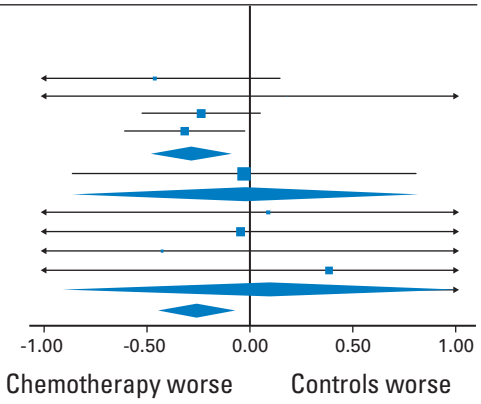

Fig 3. Forest plot of effect sizes (*g*) for studies assessing visuospatial ability. Chemo, chemotherapy; R-BANS, Repeatable Battery of Adult Neuropsychological Status; WAIS-III, Wechsler Adult Intelligence Scale–III.

education are known to be associated with cognitive functioning. Nevertheless, most samples reported that patients were on average in late middle age and had 1 to 3 years of education after high school, so there may not have been enough variability to yield significant findings. The lack of time since chemotherapy as a significant moderator suggests that cognitive improvement remains relatively stable ≥ 6 months after chemotherapy. Few studies have examined longitudinal change in cognitive function in the postchemotherapy period. Evidence is mixed, with some data suggesting improvements over time,[8,53] whereas others report cognitive decline.[7] Additional research is needed to understand longitudinal change in cognitive functioning after treatment completion. The finding that endocrine therapy is not a significant moderator of cognition is perhaps not surprising in light of conflicting previous findings. Previous studies have generally observed significant cognitive deficits when comparing patients with breast cancer treated with endocrine therapy with noncancer controls,[22,58,59] but not when comparing them with patients with breast cancer treated without endocrine therapy.[53,60] Recent data suggest that tamoxifen, but not aromatase inhibitors, may adversely affect cognitive function.[22] When we restricted moderation analyses to examine patients receiving tamoxifen (ie, not aromatase inhibitors), results remained nonsignificant. Therefore, our meta-analysis is consistent with studies finding no effect of endocrine therapy on postchemotherapy cognitive functioning.[53,61]

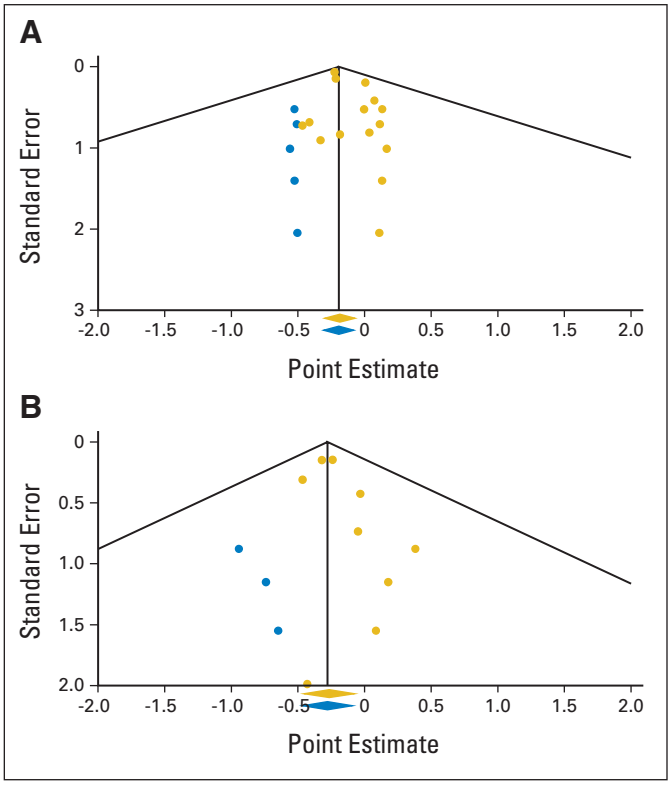

Fig 4. (A) Funnel plot of effect sizes by standard error for verbal ability. (B) Funnel plot of effect sizes by standard error for visuospatial ability. Observed comparisons are represented by gold circles, while imputed comparisons are represented by blue circles.

The quality of a meta-analysis depends on the quality of the studies analyzed. Studies included in the current meta-analysis are characterized by several strengths, such as use of well-known and well-validated tests of cognitive function. In addition, eight of the 17 studies featured longitudinal comparisons with a prechemotherapy baseline. Nevertheless, several limitations are evident in existing literature. For example, sample sizes tended to be small, ranging from 18 to 97 participants treated with chemotherapy. In addition, of the 13 studies that compared patients treated with chemotherapy with controls (ie, local therapy or no cancer), only six studies matched patients and controls on relevant variables such as age and education. Nevertheless, as recent improvements in methodologic quality (eg, longitudinal designs, large samples, matched controls) become the norm, the quality of meta-analyses will improve as well.

Publication bias is a common concern in meta-analysis. The current study addressed this issue with funnel plots and trim-and-fill procedures. Results demonstrated slight bias in analysis of visuospatial ability, but in the opposite direction than would be expected from publication bias. This finding may reflect the current state of the science. Because chemobrain is commonly reported by cancer survivors and research on the topic is relatively new, manuscripts that report null results are likely to be of interest to peer-reviewed journals. Alternately, observed bias may result from another cause, such as

sampling variability. In any case, effect size estimates adjusted for bias were within the CIs of the unadjusted estimates. As such, they did not alter our study conclusions regarding the presence of small but statistically significant deficits in verbal ability and visuospatial ability in patients previously treated with chemotherapy.

There are several clinical and research implications of the current meta-analysis. Clinically, our findings suggest that patients with breast cancer considering chemotherapy be educated that ≥ 6 months after treatment, they can expect normal cognitive functioning with the exception of slight impairments in verbal abilities (eg, word-finding difficulty) and visuospatial abilities (eg, getting lost more easily). There may be considerable variability in cognitive outcomes, however, with some patients reporting no impairments and others reporting more severe or pervasive deficits. Patients treated with chemotherapy reporting cognitive difficulties should be referred to a neuropsychologist for evaluation and management of cognitive deficits.[62,63] Management of cognitive deficits typically involves developing awareness of situations in which cognitive difficulties are likely to arise and rehearsing compensatory strategies.[62] Preliminary research suggests that these strategies result in moderate to large improvements (ie, 0.5 to 1.0 standard deviations) in objective neuropsychological function and self-reported cognition after cancer treatment.[62] Regarding research implications, it should be noted that included studies focused on patients who remained disease-free after treatment. Cognitive functioning in recurrent and advanced cancer should also be studied. Finally, a wide variety of neuropsychological tests were used, which may contribute to error variance and type II error. Efforts should be made to develop a core set of neuropsychological tests to be used across studies to facilitate interpretation and meta-analysis.[64] Together, these clinical and research efforts will help breast cancer survivors achieve the best possible cognitive functioning after completion of chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Final approval of manuscript: All authors

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