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The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: A meta-analysis of the current literature

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Abstract

Objective: Several studies have identified that adjuvant chemotherapy for breast cancer is associated with cognitive impairment; however, the magnitude of this impairment is unclear. This study assessed the severity and nature of cognitive impairment associated with adjuvant chemotherapy by conducting a meta-analysis of the published literature to date.

Method: Six studies (five cross-sectional and one prospective) meeting the inclusion criteria provided a total of 208 breast cancer patients who had undergone adjuvant chemotherapy, 122 control participants and 122 effect sizes (Cohen's *d*) falling into six cognitive domains. First, the mean of all the effect sizes within each cognitive domain was calculated (separately for cross-sectional and prospective studies); second, a mean effect size was calculated for all of the effect sizes in each cross-sectional study; and third, regression analyses were conducted to determine any relationships between effect size for each study and four different variables.

Results: For the cross-sectional studies, each of the cognitive domains assessed (besides attention) showed small to moderate effect sizes (−0.18 to −0.51). The effect sizes for each study were small to moderate (−0.07 to −0.50) and regression analysis detected a significant negative logarithmic relationship ($R^2 = .63$) between study effect size and the time since last receiving chemotherapy. For the prospective study, effect sizes ranged from small to large (0.11–1.09) and indicated improvements in cognitive function from the beginning of chemotherapy treatment to 3 weeks and even 1 year following treatment.

Conclusion: This meta-analysis suggests that cognitive impairment occurs reliably in women who have undergone adjuvant chemotherapy for breast cancer but that the magnitude of this impairment depends on the type of design that was used (i.e., cross-sectional or prospective). Thus, more prospective studies are required before definite conclusions about the effects of adjuvant chemotherapy on cognition can be made.

Keywords: Breast cancer; Adjuvant chemotherapy; Meta-analysis; Cognitive performance

1. Introduction

Chemotherapy is used widely as adjuvant therapy for breast cancer (Eifel et al., 2001). Many of the side effects of adjuvant chemotherapy are well understood and include nausea, vomiting, loss of appetite, hair loss, neutropenia, fatigue, impaired sexual function and premature menopause (Coates et al., 1983; Dorval, Maunsell, Deschenes, Brisson, & Masse, 1998; Green, Nail, & Fieler, 1994; Kaplan, 1992). However, two lines of evidence suggest strongly that chemotherapy may also disrupt central nervous system (CNS) function. First, women receiving adjuvant chemotherapy often

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report difficulties with memory, thinking clearly and concentrating (Berglund, Bolund, Fornander, Rutqvist, & Sjoden, 1991; Chemobrain; Phillips & Bernhard, 2003). Second, several studies comparing objectively measured cognitive function between women who had undergone adjuvant chemotherapy and matched controls have identified significant cognitive impairments in the chemotherapy groups (Ahles et al., 2002; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998; Wieneke & Dienst, 1995). Finally, a recent prospective study of the effects of adjuvant chemotherapy on cognitive function has reported that cognitive performance does not decline after 3 weeks or 1 year of chemotherapy when analysed at a group level. However, when examined at an individual level, some patients do show a significant deterioration in their performance following adjuvant chemotherapy (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004).

While cognitive impairment has been observed in each cross-sectional neuropsychological study of chemotherapy conducted to date, several recent reviews have highlighted serious methodological weaknesses in each (Bender, Paraska, Sereika, Ryan, & Berga, 2001; Ganz, 1998; Olin, 2001; Phillips & Bernhard, 2003; Schagen et al., 2002a, Schagen, Muller, Boogerd, & van Dam, 2002b). These are due mainly to the use of cross-sectional experimental designs. Specifically, inferences about cognitive impairment based on such designs are limited by heterogeneity in the types of chemotherapy given and in the length of time since the completion of chemotherapy in the patient groups, failure to control for the potential effects of mood, menopause or adjuvant hormonal therapy on cognitive function, relatively small sample sizes and a large number of tests given in each study without consideration of Type I error rates (Bender et al., 2001; Ganz, 1998; Olin, 2001; Phillips & Bernhard, 2003; Schagen et al., 2002a, 2002b). Despite these different weaknesses, each reviewer recommends that there is sufficient *prima facie* evidence that cognitive impairment is associated with adjuvant chemotherapy and that this area should be the subject of further investigation.

One important aspect of the data that has been overlooked by all reviews of the literature to date is the magnitude of the cognitive impairment observed in breast cancer patients treated with adjuvant chemotherapy. For example, all cross-sectional studies to date have based their conclusions about the nature and severity of chemotherapy-related cognitive impairment on patterns of statistically significant differences between chemotherapy and control groups. However, statistical significance indicates only the probability of incorrectly rejecting statistical hypotheses and provides no information about the severity or importance of any cognitive impairment (Cohen, 1994; Zakzanis, 2001). In order to understand the magnitude of cognitive impairment found in cross-sectional studies, it is necessary to express any differences in averages between chemotherapy groups and matched controls as a function of the variance in each group (i.e., statistical effect size; Cohen, 1988). For prospective designs, it is necessary to express the difference between baseline and post-chemotherapy conditions as a function of the variance in each condition in order to obtain magnitudes of change. The calculation of these effect sizes provides a framework within which to directly compare the magnitude of impairment on various aspects of cognitive function. Provided studies report (1) their sample size, and (2) group means and standard deviations for cognitive performance or summary statistics such as t, p, r or F, it is possible to estimate effect sizes for each comparison (Cooper & Hedges, 1994; Zakzanis, 2001). For the studies that have used cross-sectional designs, these effect sizes can be averaged with effect sizes derived from the same or similar tasks across each independent but comparable study. The integration of effect sizes across different studies also minimizes the extent to which errors associated with the experimental design can exert their effects on inferences about chemotherapy and cognition.

Measures of effect size indices have been used previously in a recent meta-analysis that explored the magnitude of cognitive impairment associated with chemotherapy treatments across a range of cancers, including breast cancer (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003). This meta-analysis found that cognitive impairment ranged from small to moderate and occurred most frequently in the domains of executive function, verbal memory, and motor function. However, the extent to which this broad meta-analysis analysis can be generalized to the effects of adjuvant chemotherapy in breast cancer is limited because issues such as the gender of patients, the hormonal status of patients and the chemotherapy regimens used, are specific to breast cancer. When considered together, these issues indicate that it is both worthwhile and important to conduct a meta-analysis that is restricted to the effects of adjuvant chemotherapy on cognitive performance in women with breast cancer. Admittedly, this literature is still small and there exist only a few studies for the meta-analysis. However, an integration of the published data will increase general understanding of the nature and severity of cognitive impairment specific to breast cancer, provide a foundation for the design of future studies of cognitive function in adjuvant chemotherapy, provide a framework for interpretation of the importance of newer experimental results, and illustrate the importance of presenting complete summary and statistical data in studies.

The overarching aim of the current study was therefore to determine the nature and severity of the cognitive

impairment associated with adjuvant chemotherapy. Specifically, the first aim was to estimate the magnitude of cognitive impairment associated with adjuvant chemotherapy by expressing differences in performance on the different measures either between chemotherapy and control groups (i.e., as in cross-sectional studies) or baseline and chemotherapy conditions (i.e., as in prospective studies) using measures of effect size. The second aim was to determine whether specific brain systems are more susceptible to chemotherapy-related disruption than others by comparing the magnitude of impairment between the different cognitive domains that have been assessed. The third aim was to determine whether there were any relationships between the magnitude of cognitive impairment and factors relating to treatment or demographic characteristics of the different patient groups studied.

2. Method

2.1. Literature search

PsychINFO and MEDLINE databases were searched using the keywords *breast cancer*, *chemotherapy and cognition*, *cognitive*, *neuropsychology* or *neuropsychological* for the period from January 1980 to December 2004. This search identified nine cross-sectional studies, three prospective studies, and also five reviews that provided reference lists that were scrutinized to capture studies that may have been missed in the database search. A total of 10 sets of cognitive function comparisons between an adjuvant chemotherapy and a control group were identified from a total of nine studies (Ahles et al., 2002; Berglund et al., 1991; Brezden et al., 2000; Castellon et al., 2004; Schagen et al., 1999, 2001, 2002a, 2002b; Tchen et al., 2003; van Dam et al., 1998; Wieneke & Dienst, 1995). For a set of comparisons to be included in the current meta-analysis, it was necessary that: (1) the treatment group consisted solely of patients receiving or having received adjuvant chemotherapy for breast cancer; (2) at least one objective and validated neuropsychological measure was used; and (3) sufficient statistics for computation of effect sizes were reported (i.e., means and standard deviations or t, r, p or F and sample sizes). Using these criteria, two sets of comparisons were excluded because they used only subjective or electrophysiological measures (Berglund et al., 1991; Schagen et al., 2001). Another two sets of comparisons were excluded because they did not provide summary data for cognitive performance in either the chemotherapy or control groups and therefore effect sizes could not be calculated (Schagen et al., 2002a, 2002b; Tchen et al., 2003). Another set was excluded because it reported only non-parametric p values that could not be converted accurately to estimates of effect size (Brezden et al., 2000). The remaining six sets of comparisons met the inclusion criteria, and these were derived from five cross-sectional studies and one prospective study (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995). The baseline comparison of patients to controls from the prospective study of chemotherapy could not be included in the cross-sectional analysis, as summary data were not provided for the controls. Thus, the cross-sectional studies provided a total of six different chemotherapy patient groups totalling 208 participants and three different control groups totalling 122 participants. These studies yielded a total of 122 effect sizes falling into six cognitive domains. As the methods, design and limitations of each of these studies have been previously considered (Bender et al., 2001; Ganz, 1998; Phillips & Bernhard, 2003), the current analysis focused only on measures of effect size. Of the three prospective studies that were identified, one was excluded because it provided no statistical summary data (O'Shaughnessy, 2002) and another was excluded because it presented only two cases and did not compare their cognitive performance using any statistical methods (Paraska & Bender, 2003). The remaining prospective study (Wefel et al., 2004) yielded 30 effect sizes, half indicating the magnitude of change from baseline to 3 weeks post-chemotherapy and half indicating change from baseline to 1-year post-chemotherapy.

2.2. Calculation of effect sizes

The magnitude of difference between sample means for each test in each study was expressed using Cohen's d (Cohen, 1988). Cohen's d is based on the difference between means expressed as a function of the pooled standard deviation of both groups.

$$\text{Cohen's } d = [M_1 - M_2]/\mathrm{SD}_{\text{pooled}} \quad \text{where}$$
$$\mathrm{SD}_{\text{pooled}} = \mathrm{SD}_1 + \mathrm{SD}_2/2(\text{equal } N \text{ in each group}),$$
or
$$\mathrm{SD}_{\text{pooled}} = \sqrt{(N_1 - 1)\mathrm{SD}_1^2 + (\mathrm{N}_2 - 1)\mathrm{SD}_2^2} \\ /N_1 + N_2 - 2(\text{unequal } N \text{ in each group}) \quad (1)$$

and where M_1 = mean of the chemotherapy group, M_2 = mean of the control group, SD_1 = standard deviation of the chemotherapy group, SD_2 = standard deviation of the control group. $\mathrm{SD}_{\text{pooled}}$ = pooled standard deviation, N_1 = sample size of the chemotherapy group, and N_2 = sample size of the control group.

Three studies provided means and standard deviations (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998) that were used to calculate Cohen's d. One study provided Hedge's g (Wieneke & Dienst, 1995), which was transformed into Cohen's d using the

formula: $g\sqrt{dfwithin/N}$. For all cognitive tests the direction of differences was standardized so that a negative effect size indicated that performance in the chemotherapy group was worse than controls.

2.3. Neuropsychological tests

Fifty-five independent neuropsychological test measures were used across all six studies. These tests were classified into six cognitive domains according to the particular cognitive function each test measured according to our own clinical practice (Maruff, Currie, McArthur-Jackson, Mulhall, & Benson, 1994) and the classifications used in compendiums of neuropsychological tests (Lezak, 1995). The classification of tests according to cognitive domain is shown in Table 1. Although most neuropsychological tests are considered to measure multiple cognitive functions, each test was included only once in what was deemed to be the most appropriate cognitive domain to avoid over-inflation of mean effect sizes in this meta-analysis. A test of homogeneity of effect sizes in each cognitive domain was conducted in order to confirm that the neuropsychological tests were measuring common parameters. The percentage of the effect sizes estimated for each domain from the cross-sectional studies were as follows: attention, 29.51%; executive function, 25.41%; memory, 28.68%; motor function, 9.84%; language, 2.46%; and spatial ability, 4.10%. For the prospective study, the percentage of effects sizes were: attention, 20.00%; executive function, 33.33%; memory, 26.66%; motor function, 13.33%; language, 0.00%; and spatial ability, 6.67%.

2.4. Analysis

2.4.1. Cross-sectional studies

First, a mean effect size for each cognitive domain was calculated (i.e., the mean of all of the effect sizes across the five studies within each cognitive domain). In order to derive unbiased mean effect sizes for each domain, each individual effect size was weighted according to the same size of the groups from which it was derived using the following formula: $d = \Sigma wd/\Sigma w$, where $w = 2N/‘8 + d^2$, where $N =$ sample size of experimental and control group combined (Wolf, 1986). In order to appreciate the meaning of these weighted average effect sizes, an overlap statistic was also calculated for each domain (Cohen, 1994). The severity of cognitive impairment in each domain was compared by submitting the effect sizes in each of the domains to an analysis of variance (ANOVA).

Second, since ANOVA indicated that effect sizes were of equivalent magnitude across the cognitive domains with the exception of attention (see Section 3), a general effect size was calculated for each study. This general effect size included only motor function, memory and executive function, as the average effect sizes for the language and spatial ability domains were considered to be less reliable due to the small number of effect sizes from which they were derived. Regression analyses were then conducted to investigate whether there were any relationships between the general effect size for each study, the average time since last receiving chemotherapy, the percentage of patients currently taking tamoxifen, the percentage of patients previously taking tamoxifen, the average of the patient groups, and chemotherapy regimen.

Table 1
Cognitive domains assigned to the neuropsychological tests used in the studies of adjuvant chemotherapy

Domain	Neuropsychological tests
Attention	Paced Auditory Serial Addition Test, Trails A, Correct Continuous Performance Test (CPT) Distractibility—No. Targets, Vigilance—No. Targets Correct (CPT), Distractibility—Reaction Time (CPT), Vigilance-Reaction Time (CPT), D2 (GZ-F score), Fepsy Visual Reaction (dominant), Fepsy Visual Reaction (non-dominant), Fepsy Binary Choice, Fepsy Visual Searching, Digit Span—forwards (WAIS), WAIS-R Arithmetic, CalCAP Median SRT, CalCAP Median CRT, CalCAP Accuracy
Memory	California Verbal Learning Test (CVLT) 1–5, Short Delay Free Recall (CVLT), Long Delay Free Recall (CVLT), List A—Total No. Correct and Long Delay Recall (CVLT), List B—Total No. Correct and Long Delay Recall (CVLT), Long Delay Recognition (CVLT), REY Complex Figure Test Recall, Logical Memory I Stories A and B (WMS-R), Logical Memory II Stories A and B—30 min delay (WMS-R), Visual Reproduction I (WMS-R), Visual reproduction II—30 min delay (WMS-R), REY 15 Words Test Recall, REY 15 Words Test—Recognition, REY 15 Words Test—Delayed Recall, REY Complex Figure Recall, Immediate Recall (WMS), Delayed Recall (WMS), VSRT Long-Term Storage and Delayed Recall, NVSRT Long-Term Storage and Delayed Recall
Motor function	Grooved Peg Board (dominant), Grooved Peg Board (non-dominant), Thumb–finger sequences (right hand), Thumb–finger sequences (left hand), Fepsy Finger Tapping (right or dominant), Fepsy Finger Tapping (left or non-dominant)
Executive function	Digit Symbol (WAIS-R) and (WAIS III), Trails B, Categories Short Booklet, Similarities (WAIS-R), Controlled Oral Word Association Test, Word Fluency Sub-Test Dutch Aphasia Society, Animal Fluency, Stroop Test, Digit Span—backwards (WAIS)
Spatial ability	REY Complex Figure Test—Direct Copy, Block Design (WAIS-R) and (WAIS III)
Language	Boston Naming Test, Reading Subtest (WRAT-R)

2.4.2. Prospective study

A mean effect size for each cognitive domain was calculated, which indicated the magnitude of performance change from baseline to short-term post-chemotherapy and baseline to long-term post-chemotherapy.

3. Results

3.1. Cross-sectional studies

The average age of participants in the combined meta-analytic sample was 48.1 years in the chemotherapy group and 51.97 in the control group. From studies that reported menopausal status, approximately 98% of chemotherapy patients and 38% of controls were post-menopausal at the time of cognitive testing. Three studies did not report menopausal status (Ahles et al., 2002; Castellon et al., 2004; Wieneke & Dienst, 1995). Across all the studies, 48.4% of chemotherapy patients were taking tamoxifen at the time of cognitive testing and at least 16% had previously taken tamoxifen but had ceased at some stage prior to testing. The most common chemotherapy regimen was cyclophosphamide/methotrexate/5-fluorouracil (CMF) with 38.46% of all participants having been administered this combination, followed by 5-fluorouracil/epidoxorubicin/cyclophosphamide (FEC; 19.46%), cyclophosphamide/thiotepa/carboplatin (CTC) coupled with FEC (18.10%), cyclophosphamide/doxorubicin/5-fluorouracil (CAF; 8.15%), cyclophosphamide/doxorubicin (CA; 6.34%), CMF coupled with CAF (3.17%) and 4.53% received other regimens. There were 87.33% of patients who received 5-fluorouracil (5-FU) as part of their treatment. The average time period since last receiving chemotherapy treatment across all chemotherapy groups was 3 years with intervals ranging from 5 months to 10 years.

Table 2 shows the weighted average effect sizes for each cognitive domain. Using the conventions of Cohen (1994), the effect sizes for each domain were small to moderate (i.e., between −0.03 and −0.51). The overlap statistics for each domain effect size indicated that this impairment corresponded to a percentage overlap between control and chemotherapy groups of between 66 and 99%. ANOVA indicated a significant difference between the effect sizes in each domain [$F(5,116) = 3.289$, $p = .008$; see also Fig. 1]. Post hoc tests indicated that the average effect size obtained for the attention domain was significantly smaller than the average effect size obtained for the memory ($p = .008$), motor function ($p = .013$) and spatial ($p = .004$) domains although there as no difference in average effect size between these three domains. The Levene statistic test of homogeneity of effect sizes indicated that the error variance across each group was equal, [$F(5,116) = 1.938$, $p = .093$].

Table 3 outlines the general effect size for each study (that included only motor function, memory and executive function effect sizes). These varied between a small (−0.071) to moderate (−0.495) impairment. Table 3 also shows the average time since last chemotherapy treatment, the percent of patients with current or previous tamoxifen use, chemotherapy regimens and the average age of participants in each study. Correlation of each individual study's effect size on each of these variables indicated a significant logarithmic relationship between effect size and time since last chemotherapy treatment ($R^2 = .63$; see Fig. 2), effect size and percentage of patients currently taking tamoxifen ($R^2 = .60$; see Fig. 2), and effect size and average age ($R^2 = .67$; see Fig. 2). No relationship was detected between the percentage of patients previously on tamoxifen and cognitive performance.

3.2. Prospective study

Table 4 shows the average effect sizes for each cognitive domain obtained from the prospective study. Using the conventions of Cohen (1994), the effect sizes for each domain were small to large at the short-term post-chemotherapy follow-up (i.e., between 0.11 and 1.09) and at the long-term post-chemotherapy follow-up (i.e., between 0.18 and 0.71). The overlap statistics for each domain effect size indicated that this impairment corresponded to a percentage overlap between baseline and short-term post-chemotherapy conditions of between 41.45 and 91.6% and a percentage overlap between baseline and long-term post-chemotherapy conditions of between 56.56 and 86.7%. ANOVA indicated no significant difference between the effect sizes

Table 2
Results of meta-analysis: magnitude of impairment averaged for each cognitive domain

Cognitive domain	*N* Effect sizes	*N* Chemo patients	*N* Controls	Average effect size (Cohen's *d*)	Overlap statistic (%)
Attention	36	208	122	−0.03	98.46
Motor function	12	172	103	−0.51	66.12
Memory	35	208	122	−0.26	81.34
Executive function	31	208	122	−0.18	86.70
Language	3	35	35	−0.41	72.00
Spatial ability	5	99	54	−0.48	67.80

Note: *N*, number.

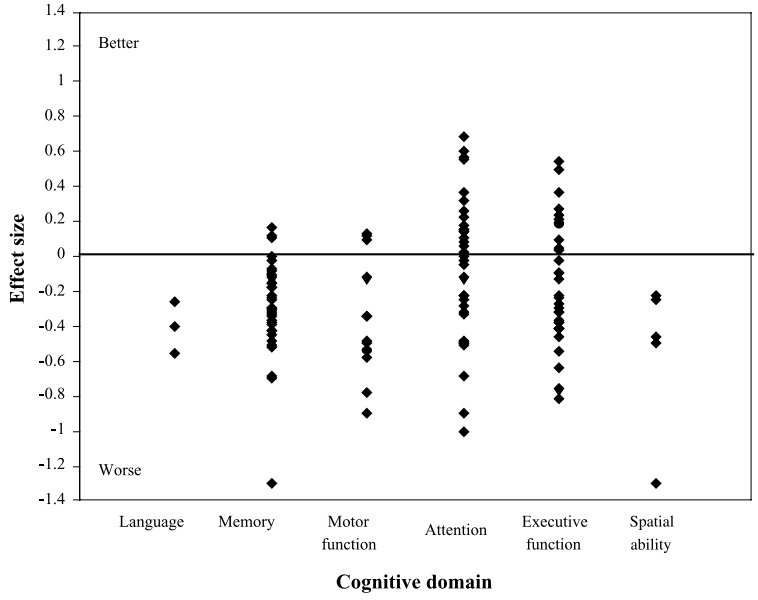

Fig. 1. The effect sizes obtained for each cognitive domain.

Table 3
Magnitude of general cognitive impairment detected for each study

Study	General effect size[a]	Average time since last chemotherapy (years)	Percent currently on tamoxifen	Percent previously on tamoxifen	Average age (years)	Type of chemotherapy used (percent of group treated)
Ahles et al. (9)	−0.071	9.4	9	37	59	CMF (40), CAF (40), Other[b] (20)
Castellon et al. (25)	−0.220	3.5	9	n/r	47	CMF (41), CMF+A (38), ACT (9), Other (12)
Schagen et al. (13)	−0.223	1.9	46	5	47	CMF (100)
Van Dam et al. (11)	−0.500	1.6	85	15	46	High dose CTC (100)
	−0.222	1.9	7	22	48	FEC (100)
Wieneke and Dienst (12)	−0.430	0.5	39	n/r	42	CMF (61), CAF (14), CMF/CAF (25)

[a] Includes only memory, executive function and motor function. CMF, cyclophosphamide/methotrexate/fluorouracil; A, doxorubicin; FEC, fluorouracil/epidoxorubicin/cyclophosphamide; CTC, cyclophosphamide/thiotepa/carboplatin; CAF, cyclophosphamide/doxorubicin/fluorouracil; ACT, doxorubicin/cyclophosphamide.

[b] Other, cyclophosphamide/doxorubicin, cyclophosphamide/methotrexate/fluorouracil/vincristine/prednisone and cyclophosphamide/carboplatin; Other, specific dose not reported.

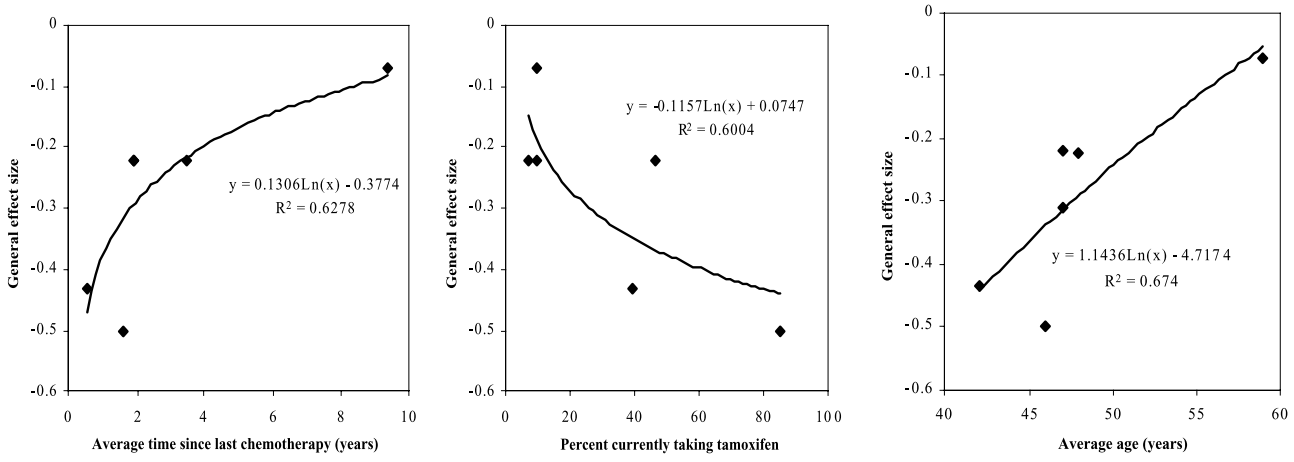

Fig. 2. The relationship between the magnitude of impairment and the number of years since chemotherapy treatment, the percentage of patients currently taking tamoxifen, and average age (in years).

Table 4
Results from a prospective study: magnitude of impairment averaged for each cognitive domain

Cognitive domain	*N* Effect sizes	Short-term follow-up			Long-term follow-up		
		Average effect size (Cohen's *d*)	SD	Overlap statistic (%)	Average effect size (Cohen's *d*)	SD	Overlap statistic (%)
Attention	3	1.09	1.36	41.45	0.71	1.03	86.7
Motor function	2	0.11	0.31	91.6	0.18	0.23	56.56
Memory	4	0.36	0.27	75.04	0.48	0.03	67.8
Executive function	5	0.39	0.33	73.21	0.51	0.44	66.12
Language	—	—	—	—	—	—	—
Spatial ability	1	0.31	—	78.09	0.38	—	73.82

Note: *N*, number; SD, standard deviation.

in each domain at either the short-term post-chemotherapy follow-up [$F(4,10) = 0.86$, $p = .519$] or the long-term post-chemotherapy follow-up [$F(4,10) = 0.31$, $p = .868$]. The Levene statistic test of homogeneity of effect sizes indicated that the error variance across each group was significantly different between the short-term follow-up [$F(4,10) = 5.73$, $p = .012$] and the long-term follow-up [$F(4,10) = 6.08$, $p = .010$].

4. Discussion

The current meta-analysis sought to determine the nature and severity of the cognitive impairment associated with adjuvant chemotherapy for breast cancer. Analysis of the cross-sectional studies suggests that although cognitive impairment occurs reliably in women who have undergone adjuvant chemotherapy for breast cancer, the magnitude of this impairment is small to moderate. Specifically, the magnitude of impairment ranged from −0.03 to −0.51 of a standard deviation below matched controls. While the greatest impairments were detected in the domains of language and spatial function, these effect sizes were based on a very small number of comparisons (i.e., 3 and 5, respectively). Therefore, they are likely to be much less reliable than the effect sizes estimated for psychomotor function, attention, executive function and memory that ranged from −0.03 to −0.35, which were derived from relatively large numbers of participants (340 participants), and a larger number of individual effect sizes. These more reliable effect sizes are small to moderate in nature, as defined by Cohen (1988); however, the clinical relevance of these indices are best understood with reference to the overlap statistic (Zakzanis, 2001). For example, the effect size of −0.26 detected for the memory domain indicates that there is approximately 81% overlap between the distributions of memory function in adjuvant chemotherapy groups and cancer controls.

Another way of considering the magnitude of impairment is with reference to the effect of a factor that can influence cognitive performance, such as fatigue, and is relatively well understood at all levels of the community. In recent studies, we measured the effect of fatigue on cognitive function in healthy adults (Falleti, Maruff, Collie, Darby, & McStephen, 2003; Maruff, Falleti, Collie, Darby, & McStephen, 2005). With 24 h of sustained wakefulness, the effect size describing the magnitude of impairment in psychomotor and memory functions was −1.2 (Falleti et al., 2003). An effect size of −0.3 occurred in the healthy adults after they had been awake continuously for 12 h, and an effect size of −0.4 was observed after 16 h of sustained wakefulness (Maruff et al., 2005). Therefore, in using this comparison, the severity of cognitive impairment associated with adjuvant chemotherapy is seen to be equivalent to that associated with the fatigue that occurs at the end of a normal day (e.g., after being awake for around 12 h).

Interestingly, the current analysis of cross-sectional studies indicates that the magnitude of impairment is very small for the attention domain (see Table 2). Upon closer inspection of the effect sizes that were generated, it can be seen that the patients treated with chemotherapy scored better than the comparison group on some tests and on other tests they scored worse (see Fig. 1). There are three possible reasons for this: (1) the methodological limitations inherent in each of the studies (see Phillips & Bernhard, 2003) that these effect sizes were generated from could have affected the detection of any impairment that should have been found; (2) only some aspects of attention are adversely affected by the adjuvant chemotherapy treatment process; or (3) only a subset of patients show an impairment in cognitive function due to particular factors associated with the adjuvant chemotherapy process (e.g., menopausal status, anemia). Therefore, it is necessary to investigate which of these possibilities has contributed to the varied results that have been obtained concerning the attentional cognitive domain.

The analysis also indicates that, with the exception of attention, adjuvant chemotherapy affects each cognitive domain that was assessed to approximately the same extent (see Table 2). This suggests that chemotherapy may give rise to some generalized cognitive impairment. This is consistent with a recent study that was conducted, which also found that patients being treated with

chemotherapy showed poorer cognitive function globally when compared with age- and education-matched controls (Tchen et al., 2003). When general effect sizes were calculated for only motor, executive function and memory in the current study, the magnitude of impairment associated with adjuvant chemotherapy appears to be less when the time since chemotherapy increases (see Fig. 2). Although cognitive impairment is still detectable at an average of nine years post-treatment, it is very mild (see Table 3 and Fig. 2). The analysis also shows that the magnitude of impairment for these cognitive functions is smaller in studies where a fewer percentage of participants are currently taking tamoxifen, but larger in younger age groups (see Table 3 and Fig. 2). However, further studies are required in order to investigate these relationships further and determine why they occur.

The current meta-analysis of cross-sectional studies does not avoid the methodological limitations operating in each individual study (Bender et al., 2001; Ganz, 1998; Phillips & Bernhard, 2003). It does, however, minimize the influence of errors in experimental design on the overall conclusion that adjuvant chemotherapy does affect cognition because such errors are averaged out with the computation of average effect sizes both between and within studies. The wide ranges in effect sizes detected for each cognitive domain (Table 1) most probably reflects these different aspects of experimental design. Therefore, the average estimates derived from the large number of comparisons and relatively large total sample size in the current meta-analysis provides a more reliable indication of the cognitive impairment associated with adjuvant chemotherapy when women are compared to some non-chemotherapy control group. The one prospective study considered in the meta-analysis suggests that there is no specific chemotherapy-related cognitive impairment; however, this result requires replication before there can be reliable comparison of the results of cross-sectional and prospective studies of the same issue.

Unfortunately, some of the studies identified in the literature could not be included in the meta-analysis because they did not provide information to allow the computation of effect sizes (Berglund et al., 1991; Brezden et al., 2000; Schagen et al., 2001, 2002a, 2002b; Tchen et al., 2003). However, it is possible to consider their conclusions qualitatively against the quantitative framework provided by the meta-analysis. First, two studies that did not meet the inclusion criteria here also observed that, when compared to healthy controls, women with breast cancer undergoing adjuvant chemotherapy showed cognitive impairments that were both subtle and general across domains of memory, motor function and executive function (Brezden et al., 2000; Tchen et al., 2003). Although they did not compare group performance measures, Wefel et al. (2004) reported that the incidence of cognitive impairment in women with breast cancer prior to the initiation of chemotherapy was greatest on tests of verbal learning, executive, motor function and memory. Interestingly, in all three of these studies, there was evidence to suggest that attentional function was the least impaired of the cognitive domains assessed, as was found in the current meta-analysis. For example, Tchen et al. (2003) reported that performance on the Connor's Continuous Performance Test (CPT) and the Trail-Making Tests was not significantly different between women receiving CAF chemotherapy and well-matched healthy controls (although no means or even statistics were reported to support this conclusion). In addition, this study and another (Brezden et al., 2000) report that scores for attentional domain of the High-Sensitivity Cognitive Screen (HSCS) were not significantly different between chemotherapy patients and controls. Finally, Wefel et al. (2004) also found no differences between controls and patients in the incidence of impaired scores on the Trail-Making and Digit Symbol Substitution Tests.

The meta-analysis also concluded that the moderate effect size observed for spatial function was unreliable because it was based on only a few effect sizes computed from small numbers of subjects. Consistent with this, the studies of both Brezden et al. (2000) and Tchen et al. (2003) found no differences between breast cancer patients and controls in measures of spatial function. The meta-analysis also suggested that the severity of cognitive impairment decreased as the time since cessation of chemotherapy increased. This was examined in one cross-sectional study that could not be included in the meta-analysis because it analysed only the incidence of cognitive impairment in women with breast cancer 4 years adjuvant chemotherapy had ceased (Schagen et al., 2002a, 2002b). They found that the incidence of cognitive impairment in the chemotherapy group was less than that observed in the same group assessed 2 years post-chemotherapy. Therefore, when considered together, the results of the studies that did not meet the current inclusion criteria appear qualitatively similar to those of the current meta-analysis.

Finally, analysis of the group data obtained from the only prospective study of the effects of chemotherapy on cognitive function conducted to date indicates that the women receiving adjuvant chemotherapy actually showed substantial improvement in attentional, executive and memory function post-chemotherapy (see Table 4). Thus, the results of this group analysis are inconsistent with the conclusions of most cross-sectional studies. The improvement in cognitive function observed may indicate that adjuvant chemotherapy is beneficial to the CNS in women with breast cancer. This may be because the initiation of curative treatment acts to reduce the psychological burden, stress and depression associated with a diagnosis of breast cancer. If this is the case, the general and subtle impairments in

cognitive function observed when chemotherapy groups are compared to healthy controls may actually reflect other non-chemotherapy-related factors such as illness variables, mood variables or hormonal status of women. Alternatively, the improvement in cognitive function may have been due to methodological limitations associated with the prospective study designs, such as the presence of practice effects in their cognitive tests (even though alternative forms were used for some instruments), or the absence of any untreated control group (Wefel et al., 2004).

The finding of improved performance following adjuvant chemotherapy in patient groups is inconsistent with the data from studies that have considered the performance of individual patients (Paraska & Bender, 2003; Wefel et al., 2004). First, a recent case-study of neuropsychological and mood function in two women prior to receiving chemotherapy, one week after the completion of chemotherapy and 12 months later suggested that performance deteriorated in both patients (Paraska & Bender, 2003). However, the authors argued that in one woman the cognitive decline was due to increased depression. Unfortunately, these conclusions were drawn on the basis of the comparison of changes in raw scores, and the potential for any error variability in performance was not considered at all (i.e., non-statistical tests were used to guide inferences). Hence, it is not possible at this stage to determine whether the cognitive decline observed was true. Despite the absence of any chemotherapy-related decline in the group cognitive function, Wefel et al. (2004) also analysed the cognitive performance of individual patients. Here, the difference between the pre- and post-chemotherapy assessment was expressed using a reliable change index (RCI). Chemotherapy-related cognitive decline was defined if this RCI exceeded the 90% confidence interval in the negative direction for any cognitive measure (e.g., $p < 0.05$ one-tailed). Using this definition of cognitive deterioration, 61% of women demonstrated short-term post-chemotherapy cognitive impairment. On the basis of this finding, Wefel et al. concluded that adjuvant chemotherapy was neurotoxic. However, the classification of abnormal cognitive decline in individuals on the basis of multiple tests is subject to experiment-wise error and this was not taken into account in the Wefel et al. study. Put simply, the more tests used to assess performance, the greater the probability that an individual will meet a criteria for impairment (Ingraham & Aiken, 1996). In the Wefel et al. (2004) study, the criteria for impairment was a decline of 1.65 SD (i.e., an RCI with 90% confidence intervals) on any one of 15 different performance measures. According to binomial probability tables of Ingraham and Aiken (1996), 80% of individuals for whom there has been no true cognitive impairment will meet this criteria for abnormality by chance (i.e., false positive rate = 0.8). According to these same tables, the false positive rate remains unacceptably high even if criteria for cognitive decline is made more conservative so that abnormality is required on two (approximately 50%) or three tests (approximately 20%). Compared to these estimates, Wefel et al. (2004) actually found that the number of women demonstrating impairment was less than that expected by chance (e.g., 1 abnormal RCI = 61%, 2 abnormal RCIs = 11% and 3 abnormal RCIs = 11%). Therefore, it is premature to conclude that chemotherapy disrupts CNS function on the basis of the post-hoc analysis of individual cognitive performance (see Maruff & Falleti, 2004). Instead, their data suggests the sample showed normal variability in performance over time and no chemotherapy-related cognitive change, which is what was demonstrated in their group analyses. Thus, when considered together the prospective studies suggest that there is no chemotherapy-related impairment in cognitive performance in individuals or groups. However, more prospective studies are required.

The current review does contain limitations. Its main limitation is that more error may be present because the results of several studies were combined in order to generate average effect sizes. Consequently, effect sizes that were derived particularly from the cross-sectional analyses could have been underestimated. However, when considered with the prospective analyses, these magnitudes of change are different and actually show improvements. Therefore, in order to understand these differing results, the current review provides a foundation upon which future studies should be based when investigating the association between adjuvant chemotherapy and cognitive performance.

Overall, the current meta-analysis of different study designs provides evidence of different magnitudes of cognitive impairment for the same cognitive domains. While cross-sectional designs are useful in indicating differences between groups of individuals, prospective studies are more informative as they allow for within-subject comparisons as well as the examination of performance at an individual level rather than a group level. Prospective studies also have the advantage of taking into account other factors than those related to the chemotherapy treatment process, which may also influence levels of cognitive performance. As few prospective studies have been conducted to date, more are necessary in order to determine unequivocally the nature, severity and chronicity of any chemotherapy-related cognitive impairment. Given the evidence presented here, these studies should include both short- and long-term endpoints and also compare different chemotherapy regimens. These studies should use cognitive tests that are not susceptible to practice effects and utilize appropriate statistical methods that minimize false classification rates and maximise the detection of true chemotherapy-related impairment. Finally, these

studies should report all summary data, give references for normal performance levels (if such comparisons are conducted as in the Wefel et al. study), and also measure mood performance such as depression and anxiety in order to investigate whether this is related to any performance changes that are observed in women after receiving adjuvant chemotherapy for breast cancer.

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