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Chemotherapy-Induced Cognitive Impairment in Women With Breast Cancer: A Critique of the Literature

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Purpose/Objectives: To review and critique the studies that have investigated chemotherapy-induced impairments in cognitive function in women with breast cancer.

Data Sources: Published research articles and textbooks.

Data Synthesis: Although studies of breast cancer survivors have found chemotherapy-induced impairments in multiple domains of cognitive function, they are beset with conceptual and methodologic problems. Findings regarding cognitive deficits in women with breast cancer who currently are receiving chemotherapy are even less clear.

Conclusions: Although data from published studies suggest that chemotherapy-induced impairments in cognitive function do occur in some women with breast cancer, differences in time since treatment, chemotherapy regimen, menopausal status, and neuropsychological tests used limit comparisons among the various studies. Further studies need to be done before definitive conclusions can be made.

Implications for Nursing: The potential for chemotherapy-induced impairments in cognitive function may influence patients' ability to give informed consent, identify treatment toxicities, learn self-care measures, and perform self-care behaviors.

Key Points . . .

- Cognitive function is a multidimensional concept that describes the domains resulting from healthy brain performance, namely attention and concentration, executive function, information processing speed, language, visuospatial skill, psychomotor ability, learning, and memory.
- Studies that evaluated chemotherapy-induced impairments in cognitive function in women with breast cancer provide some early insights into the specific cognitive domains that are affected by chemotherapy.
- Further investigation is needed to identify the tests that are the most valid, reliable, sensitive, and specific for detecting short-term and persistent chemotherapy-induced cognitive impairments.

Breast cancer is the most common type of malignancy and the second leading cause of cancer deaths in women in the United States (Jemal et al., 2005). Advances in breast cancer treatment have increased survival, with a relative five-year survival rate of 98% for early-stage disease (Jemal et al.). The treatment of breast cancer is multimodal and includes some combination of surgery, radiation therapy (RT), chemotherapy, hormonal therapy, or biologic therapy. Each treatment modality has its own distinct side effects, with accompanying degrees of disruption in quality of life (QOL).

Although great strides have been made in eliminating (or at least decreasing) the side effects of chemotherapy, studies consistently confirm that toxicities (e.g., fatigue, infection, nausea, vomiting, diarrhea, stomatitis, alopecia, neuropathy) continue to adversely affect QOL (Cowley, Heyman, Stanton, & Milner, 2000; Fairclough, Fetting, Cella, Wonson, & Moinpour, 1999; Ganz, 2000). A toxicity that has emerged recently is impairment in cognitive function. Patients with cancer have reported increased difficulties with their abilities to remember, think, and concentrate (Bender, Paraska, Sereika, Ryan, & Berga, 2001; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Cole, Scialla, & Bednarz, 2000; Cull et al., 1996; Ganz, 1998). However, whereas cognitive impairments in children who received cranial RT or chemotherapy have been documented (Copeland et al., 1985; Copeland, Moore, Francis, Jaffe, & Culbert, 1996; Kun, Mulhern, & Crisco, 1983; Marina, 1997; Moore, Kramer, & Ablin, 1986), comparable evidence is lacking in adults.

Cognitive function is a multidimensional concept that describes the domains resulting from healthy brain performance,

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namely attention and concentration, executive function, information processing speed, language, visuospatial skill, psychomotor ability, learning, and memory (Olin, 2001; Ryan, Morrow, Bromet, & Parkinson, 1987). The purposes of this article are to review and critique the studies that have investigated chemotherapy-induced cognitive impairments in women with breast cancer.

Methods

A search was conducted on PubMed, a service of the National Library of Medicine, for January 1966–June 2004, for all research studies published in English that evaluated chemotherapy-induced impairments in cognitive function in women with breast cancer. A careful review of the reference lists for the eight studies identified (Ahles et al., 2002; Brezden et al., 2000; Freeman & Broshek, 2002; Schagen et al., 1999, 2002; Tchen et al., 2003; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004) uncovered one additional study (Wieneke & Dienst, 1995).

The review and critique of the literature are organized by domains of cognitive function to provide the evidence that exists for chemotherapy-induced impairments in each of the domains in women with breast cancer. Although some neuropsychological tests can measure more than one domain of cognitive function, for the purpose of this review, each test was assigned to a single domain. Most assignments of tests to a specific domain were done using neuropsychological assessment references (e.g., Hebben & Milberg, 2002; Lezak, Howieson, & Loring, 2004; Spreen & Strauss, 1998), whereas some assignments were made using recent meta-analyses of neuropsychological tests in cancer and HIV populations (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Reger, Welsh, Razani, Martin, & Boone, 2002).

Table 1 summarizes data from the eight cross-sectional studies and one longitudinal study that evaluated chemotherapy-induced impairments in cognitive function in women with breast cancer. Five studies evaluated breast cancer survivors who had completed chemotherapy from six-and-a-half months to 10 years earlier (Ahles et al., 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wieneke & Dienst, 1995), and four studies were done prospectively (Brezden et al., 2000; Freeman & Broshek, 2002; Tchen et al., 2003; Wefel et al., 2004). Each group of studies is critiqued, in terms of design and methodologic issues, in the narrative section of this article. The methods used and findings from each study are evaluated in terms of their contributions to the knowledge about chemotherapy-induced cognitive impairments in patients with breast cancer.

Attention and Concentration

Attention is a cognitive function of the brain that enables a person to triage relevant inputs, thoughts, and actions while ignoring those that distract or are irrelevant (Gazzaniga, Ivry, & Mangun, 2002; Grober, 2002; Heilman, Valenstein, & Watson, 1997). Concentration is the ability to focus and sustain attention (Lezak et al., 2004). Although all of the studies used neuropsychological tests to measure attention and concentration, only eight reported their findings. Of note, the findings regarding chemotherapy-induced impairments in attention and concentration are inconsistent. Only three studies found significant deficits in attention and concentration (Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995), whereas five found no deficits (Ahles et al., 2002; Brezden et al., 2000; Freeman & Broshek, 2002; Tchen et al., 2003; Wefel et al., 2004). All of the studies that found deficits were performed in survivors. In one such study (van Dam et al.), significant impairment in attention was found for high-dose but not standard-dose chemotherapy. In the only study of survivors that did not find deficits in attention (Ahles et al., 2002), survivors had been off treatment for almost 10 years, compared with studies performed with survivors who were off treatment for six months to two years (Brezden et al.; Freeman & Broshek; Schagen et al., 1999, 2002; van Dam et al.; Wieneke & Dienst). Also, different tests were used to measure attention. The only test that revealed significant deficits was the Digit Span. Tests that did not yield significant results were the D2 Test (a neuropsychological test of attention), vigilance and distractibility subtests of the Continuous Performance Test, and the attention subtests of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and High Sensitivity Cognitive Screen (HSCS).

Executive Function

Executive function refers to higher-order cognitive processes, which include initiation, planning, hypothesis generation, cognitive flexibility, decision making, regulation, judgment, feedback utilization, and self-perception (Spreen & Strauss, 1998).

All of the studies used neuropsychological tests to measure executive function, but only seven reported their findings. The findings regarding chemotherapy-induced impairment in executive function also are inconsistent. Only three studies found significant deficits in executive function (Freeman & Broshek, 2002; Schagen et al., 1999; Wefel et al., 2004), whereas four found no deficits (Ahles et al., 2002; Brezden et al., 2000; van Dam et al., 1998; Wieneke & Dienst, 1995). All of the studies that found significant deficits were performed in survivors, including two prospective studies that found significant deficits only in the survivor group (Freeman & Broshek) or after chemotherapy was completed (Wefel et al.).

The Trail Making Test-Part B, categories test, and Stroop tests demonstrated significant deficits compared to the similarities test and the self-regulation and planning subtest of the HSCS. However, why the Trail Making Test-Part B revealed significant deficits for survivors in one study (Schagen et al., 1999) but not in others (Ahles et al., 2002; van Dam et al., 1998; Wefel et al., 2004; Wienke & Dienst, 1995) is unclear. One possible explanation for the difference is the heterogeneous nature of the chemotherapy treatments that the survivors received. Additionally, the Stroop test found significant deficits for survivors in one study (Freeman & Broshek, 2002) but not in two other studies (Schagen et al., 1999; van Dam et al.). One possible explanation for the inconsistent findings is the difference in comparison groups. The study that found significant deficits compared survivors with patients who currently were receiving chemotherapy (Freeman & Broshek), whereas the studies that did not find deficits compared survivors to women who had received local therapy (i.e., surgery or RT) (Schagen et al., 1999; van Dam et al.). Although the

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Table 1. Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer

Study	Sample Characteristics	Findings	Limitations
Ahles et al., 2002 **Purpose:** to compare the neuropsychologic functioning of long-term survivors of breast cancer who were treated with standard-dose systemic chemotherapy or local therapy only **Design:** retrospective study of survivors	• N = 70: survivors = 35, controls = 35 • Mean age of survivors = 59.1 ± 10.7; controls = 60.6 ± 12.1 • Mean educational level (years): survivors = 15.2 ± 2.3; controls = 14.0 ± 2.7 • Mean time since treatment (years): survivors = 9.4 ± 4.5; controls = 9.9 ± 5.8 • Chemotherapy regimens: 40% CMF, 40% CAF, 9% AC, 9% other • 37% of the survivor group and 14% of the control group had taken tamoxifen. • No differences were found for anxiety, depression, or fatigue.	**Attention/concentration:** Continuous Performance Test vigilance and distractibility subtests: No difference was found between groups on both subtests. **Executive function:** HRNB TMT Part B: Difference between groups for this instrument was not reported. **Information processing speed:** WAIS digit symbol subtest and HRNB TMT Part A: Survivors had significantly poorer overall information processing speed compared to control group (p = 0.05). Difference between groups for each instrument was not reported. **Language:** Boston Naming Test, MAE COWA subtest, WAIS vocabulary subtest, and Wide Range Achievement Test reading subtest: No differences were found between groups in verbal ability. Differences between groups for individual instruments were not reported. **Motor function:** HRNB finger tapping subtest and thumb-finger sequencing: Survivors scored significantly lower than controls (p = 0.05). **Visuospatial skill:** WAIS block design subtest: No difference was found between groups. **Verbal memory:** CVLT and WMS logical memory subtest: No differences were found between groups on both tests. **Visual memory:** WMS visual reproduction subtest: No difference was found between groups.	• Small sample size for multiple chemotherapy regimens and variability in stage of disease and time since last treatment • Basis for Neuropsychological Performance Index was unclear, especially because group differences were evaluated with multiple thresholds. • Lacked information about menopausal status
Brezden et al., 2000 **Purpose:** to investigate whether cognitive impairment is present in women receiving standard-dose adjuvant chemotherapy for breast cancer **Design:** prospective study of patients currently receiving chemotherapy and survivors	• N = 107: on chemotherapy = 31; survivors = 40; controls = 36 • Median age: current chemotherapy = 49; survivors = 46.0; controls = 41.5 • Educational level: current chemotherapy 48% secondary, 52% postsecondary; survivors 37.5% secondary, 62.5% postsecondary; controls 36% secondary, 64% postsecondary • Median time since treatment: current chemotherapy N/A; survivors = 25 months • Chemotherapy regimen: current chemotherapy group: 39% CMF and 51% CEF; survivors: 53% CMF, 43% CEF, and 4% other • 45% of survivors were treated with tamoxifen, none in the current chemotherapy group. • No differences were found among groups for depression or anxiety.	**Attention/concentration:** HSCS attention/concentration subtest: No difference was found among groups. **Executive function:** HSCS self-regulation and planning subtest: No difference was found among groups, but a trend existed toward increased score (indicating decreased executive function) in survivors compared to controls (p = 0.07). **Information processing speed:** Not measured **Language:** HSCS language subtest: Significantly increased scores (indicating decreased language) were found in the current chemotherapy and survivor groups as compared to the control group (p = 0.03 for current chemotherapy; p = 0.05 for survivors). **Motor function:** HSCS visual motor subtest: Significantly lower scores in survivors were found compared to controls (p = 0.02). A trend existed toward decreased motor function in the current chemotherapy group compared to the control group (p = 0.09). **Visuospatial skill:** HSCS spatial subtest: No difference was found between groups. **Verbal memory:** HSCS memory subtest: Significantly decreased scores were found in the current chemotherapy group compared to the control group (p = 0.02). No difference was found between the survivor and control groups. **Visual memory:** not measured	• Multiple chemotherapy regimens, variable duration of regimens, and variability in time since last treatment • The control group had significantly younger participants compared to the current chemotherapy (p = 0.01) and survivor groups (p = 0.03) • The treatment groups (current chemotherapy, p = 0.01; survivors, p = 0.03) had significantly more postmenopausal women compared to the control group. • Information regarding fatigue was lacking.
Freeman & Broshek, 2002 **Purpose:** to determine which tools are most sensitive in detecting the effects of "chemobrain"	• N = 17: current chemotherapy = 8, survivors = 9 • Mean age: current chemotherapy = 52.6 ± 7.0, survivors = 51.1 ± 7.0 • Mean educational level: current chemotherapy = 16 ± 2.9, survivors = 17.3 ± 2.2	**Attention/concentration:** RBANS attention subtest: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. **Executive function:** HRNB TMT Part B: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported.	• Small sample size • The article compared results between current chemotherapy and survivor groups rather than test norms or a control group.

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AC—doxorubicin and cyclophosphamide; CAF—cyclophosphamide, doxorubicin, and 5-fluorouracil; CCC—cyclophosphamide, cisplatin, and carmustine; CEF—cyclophosphamide, epirubicin, and 5-fluorouracil; CMF—cyclophosphamide, methotrexate, and 5-fluorouracil; COWA—controlled oral word association; CTC—cyclophosphamide, thiotepa, and carboplatin; CVLT—California Verbal Learning Test; FEC—5-fluorouracil, epidoxorubicin, and cyclophosphamide; HRNB—Halstead-Reitan Neuropsychological Test Battery; HSCS—High Sensitivity Cognitive Screen; MAE—Multilingual Aphasia Examination; N/A—not applicable; PASAT—Paced Auditory Serial Addition Test; RAVLT—Rey Auditory Verbal Learning Test; RBANS—Repeatable Battery for the Assessment of Neuropsychological Status; RCFT—Rey Complex Figure Test; TMT—Trail Making Test; WAIS—Wechsler Adult Intelligence Scale; WMS—Wechsler Memory Scale

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Table 1. Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer *(Continued)*

Study	Sample Characteristics	Findings	Limitations
Design: prospective study of patients currently receiving chemotherapy and survivors	• Mean time since treatment: current chemotherapy group = N/A, survivors not reported (within 6–12 months) • Chemotherapy regimen: not reported • All were postmenopausal with the exception of one in the survivor group. • No difference was found between groups for depression, but a trend existed for higher scores in the survivor group (p = 0.14).	HRNB categories subtest: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. Stroop test: The survivor group scored significantly lower than the current chemotherapy group (p = 0.03). **Information processing speed:** HRNB TMT Part A: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. PASAT: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. **Language:** RBANS language subtest: No difference was found between groups, but a trend existed toward decreased scores in the current chemotherapy group as compared to survivors (p = 0.15). MAE COWA subtest: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported. **Motor function:** Grooved pegboard: No difference was found between groups, but a trend existed toward decreased score with nondominant side in the current chemotherapy group compared to survivors (p = 0.15). **Visuospatial skill:** RBANS visual-construction subtest: Significantly lower scores were found in the current chemotherapy group compared with survivors (p = 0.002). **Verbal memory:** Hopkins Verbal Learning Test: Although findings were not reported, the article implied that no difference was found between groups because the authors reported other significant findings and trends. RBANS memory subtest: No difference was found between groups, but a trend existed toward decreased scores in current the chemotherapy group with immediate memory compared to survivors (p = 0.15). **Visual memory:** WMS facial recognition subtest: Although findings were not reported, the article implied that no difference was found between groups because other significant findings and trends were reported.	• Information was lacking regarding anxiety and fatigue.
Schagen et al., 1999 **Purpose:** to examine the neuropsychological functioning of patients with breast cancer following standard adjuvant chemotherapy with CMF **Design:** retrospective study of survivors	• N = 73: survivors = 39, controls = 34 • Mean age: survivors = 47.1 ± 6.9; controls = 46.1 ± 5.2 • Educational level: survivors = 31% primary, 25% secondary, 36% university or graduate; controls = 41% primary, 41% secondary, 18% university or graduate • Mean time since treatment: 1.9 years • All were receiving CMF. • Approximately 50% were treated with tamoxifen for three years. • Survivors had significantly higher scores on the depression subscale than controls (p = 0.01).	**Attention/concentration:** WAIS digit span forward subtest: No difference was found between groups. WAIS digit span backward subtest: Survivors scored significantly lower than controls (p = 0.02). D2 Test: No difference was found between groups, but a trend existed for decreased scores in survivors (p = 0.06). **Executive function:** HRNB TMT Part B: Survivors had significantly higher scores (indicating decreased executive function) compared to controls (p = 0.01). Stroop test: No difference was found between groups. **Information processing speed:** Fepsy visual reaction (dominant): Survivors scored significantly higher (indicating decreased information processing speed) than controls (p = 0.02). Fepsy visual reaction (nondominant): Survivors scored significantly higher (indicating decreased information processing speed) than controls (p = 0.01) Fepsy binary choice and visual searching subtests: No difference was found between groups. HRNB TMT Part A: No difference was found between groups, but a trend existed for increased scores (indicating decreased information processing speed) in survivors (p = 0.08). WAIS digit symbol subtest: Survivors scored significantly lower than controls (p = 0.04).	• Significant difference between survivors and the control group in regard to educational level • All of the survivors were postmenopausal, compared to only 38% of the control group.

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AC—doxorubicin and cyclophosphamide; CAF—cyclophosphamide, doxorubicin, and 5-fluorouracil; CCC—cyclophosphamide, cisplatin, and carmustine; CEF—cyclophosphamide, epirubicin, and 5-fluorouracil; CMF—cyclophosphamide, methotrexate, and 5-fluorouracil; COWA—controlled oral word association; CTC—cyclophosphamide, thiotepa, and carboplatin; CVLT—California Verbal Learning Test; FEC—5-fluorouracil, epidoxorubicin, and cyclophosphamide; HRNB—Halstead-Reitan Neuropsychological Test Battery; HSCS—High Sensitivity Cognitive Screen; MAE—Multilingual Aphasia Examination; N/A—not applicable; PASAT—Paced Auditory Serial Addition Test; RAVLT—Rey Auditory Verbal Learning Test; RBANS—Repeatable Battery for the Assessment of Neuropsychological Status; RCFT—Rey Complex Figure Test; TMT—Trail Making Test; WAIS—Wechsler Adult Intelligence Scale; WMS—Wechsler Memory Scale

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Table 1. Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer *(Continued)*

Study	Sample Characteristics	Findings	Limitations
	• No difference was found between groups for anxiety. • No difference was found between groups, but a trend existed for higher scores on the fatigue scale for survivors (p = 0.16).	**Language:** S.A.N. word fluency subtest: Survivors scored significantly lower than controls (p = 0.03). **Motor function:** Fepsy fingertapping (dominant): Survivor group scored significantly lower than control group (p = 0.04). Fepsy fingertapping (nondominant): Survivor group scored significantly lower than control group (p = 0.003). **Visuospatial skill:** RCFT copy: No difference was found between groups. **Verbal memory:** RAVLT: No difference was found between groups for recall or recognition, but significantly lower scores were found in survivors compared to controls for delayed recall (p = 0.03). **Visual memory:** RCFT recall: Survivor group scored significantly lower than control group (p = 0.03). WMS visual reproduction subtest, immediate and delayed recall: Survivor group scored significantly lower than control group for immediate recall (p = 0.01) and delayed recall (p = 0.006).	
Schagen et al., 2002 **Purpose:** to obtain more insight into the long-term neuropsychological sequelae following chemotherapy and their course over time **Design:** retrospective study of survivors	• N = 103: survivors (high-dose chemotherapy) = 22, survivors (standard-dose chemotherapy) = 54, controls = 27 • Mean age: survivors (standard-dose chemotherapy) = 50.4 ± 5.3, survivors (high-dose chemotherapy) = 47 ± 4.8, controls = 48.8 ± 5.0 • Educational level: not reported • Mean time since treatment (years): survivors (standard-dose chemotherapy) = 3.6, survivors (high-dose chemotherapy) = 3.3 • Chemotherapy regimens: survivors (standard-dose chemotherapy) = 57% CMF, 43% FEC; survivors (high-dose chemotherapy) = FEC + CTC	**Attention/concentration:** WAIS digit span subtest and D2 Test: findings not reported **Executive function:** HRNB TMT Part B and Stroop test: findings not reported **Information processing speed:** Fepsy binary choice, visual reaction, and visual searching subtests, HRNB TMT Part A, and WAIS digit symbol subtest: findings not reported **Language:** S.A.N. word fluency subtest: findings not reported **Motor function:** Fepsy fingertapping: findings not reported **Visuospatial skill:** RCFT copy: findings not reported **Verbal memory:** RAVLT: findings not reported **Visual memory:** RCFT recall: findings not reported	• Significant differences existed in length of survival (time since treatment) between groups. • The study had sample bias because of attrition. • A lack of information regarding menopausal status existed.
Tchen et al., 2003 **Purpose:** to evaluate cognitive function, fatigue, and menopausal symptoms and to explore the relationships among them in a substantial series of patients receiving adjuvant chemotherapy for breast cancer **Design:** prospective study of patients currently receiving chemotherapy	• N = 200: current chemotherapy = 100, controls = 100 • Median age: current chemotherapy = 48, controls = 47 • Educational level: current chemotherapy = 38% secondary, 62% postsecondary; controls = 30% secondary, 70% postsecondary • Median time since treatment: N/A • Chemotherapy regimens: 64% CEF, 17% AC, 11% CMF, and 8% other • 5% of patients were taking tamoxifen. • The treatment group had signif-	**Attention/concentration:** HSCS attention/concentration subtest: No difference was found between groups, but a trend existed toward increased scores (indicating decreased attention) in the chemotherapy group compared to controls (p = 0.09). **Executive function:** HSCS self-regulation and planning subtest: No difference was found between groups, but a trend existed toward increased scores (indicating decreased executive function) in the chemotherapy group compared to controls (p = 0.09). **Information processing speed:** Not measured **Language:** HSCS language subtest: The chemotherapy group had significantly increased scores (indicating decreased language) compared to the control group (p = 0.005). **Motor function:** HSCS visual-motor subtest: No difference was found between groups. **Visuospatial skill:** HSCS spatial subtest: No difference was found between groups, but a trend existed toward decreased visuospatial skills in the chemotherapy group compared to the control group (p = 0.07).	• The study had a variability in the timing of measurement in the treatment group (36% after third, 28% after fourth, 14% after fifth, 20% after sixth, and 2% after seventh cycle). • The study accounted for fatigue, but anxiety and depression were not measured.

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Table 1. Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer *(Continued)*

Study	Sample Characteristics	Findings	Limitations
	icantly higher levels of fatigue compared to the control group ($p < 0.0001$).	**Verbal memory:** HSCS memory subtest: No difference was found between groups. **Visual memory:** not measured	
van Dam et al., 1998 **Purpose:** to assess systematically the prevalence of cognitive deficits in a group of women receiving adjuvant chemotherapy for high-risk breast cancer and to investigate whether high-dose chemotherapy impairs cognitive functioning more than standard-dose chemotherapy in this patient population **Design:** retrospective study of survivors	• N = 104: survivors (high-dose chemotherapy) = 34, survivors (standard-dose chemotherapy) = 36, controls = 34 • Mean age: survivors (high-dose chemotherapy) = 46.5 ± 6.2, survivors (standard-dose chemotherapy) = 48.1 ± 6.8, controls = 46.1 ± 5.2 • Educational level: survivors (high-dose chemotherapy) = 32% primary, 32% secondary, 36% university or graduate; survivors (standard-dose chemotherapy) = 31% primary, 25% secondary, 36% university or graduate; controls = 41% primary, 41% secondary, 18% university or graduate • Mean time since treatment (years): survivors (high dose) = 1.6, survivors (standard-dose chemotherapy) = 1.9 • Chemotherapy regimens: survivors (standard-dose chemotherapy) = four to five cycles of FEC, survivors (high-dose chemotherapy) = four cycles of FEC, then CTC • Both groups were treated with tamoxifen for two years. • Survivor (high-dose chemotherapy) group had significantly elevated scores on the depression subscale in comparison with the control group ($p = 0.041$), but not with the survivor (standard-dose chemotherapy) group. No difference was found between the survivor (standard-dose chemotherapy) and control groups. • No differences were found among three groups for anxiety.	**Attention/concentration:** WAIS digit span forward subtest: No differences were found among the three groups. WAIS digit span backward subtest: Survivor (high-dose chemotherapy) group scored significantly lower than control group ($p = 0.041$). No difference was found between survivor (high-dose chemotherapy) and survivor (standard-dose chemotherapy) or survivor (standard-dose chemotherapy) and control groups. D2 Test: No differences were found among the three groups. **Executive function:** HRNB TMT Part B: No differences were found among the three groups. Stroop test: No differences were found among the three groups. **Information processing speed:** Fepsy visual reaction (dominant): The survivor (high-dose chemotherapy) group scored significantly higher (indicating decreased information processing speed) than the control group ($p = 0.011$). No differences were found between the survivor (high-dose chemotherapy) and survivor (standard-dose chemotherapy) or survivor (standard-dose chemotherapy) and control groups. Fepsy visual reaction (nondominant): Survivor (high-dose chemotherapy) group scored significantly higher (indicating decreased information processing speed) than survivor (standard-dose chemotherapy) and control groups ($p = 0.008$). No differences were found between the survivor (standard-dose chemotherapy) and control groups. Fepsy binary choice and visual searching subtests: No differences were found among the three groups. WAIS digit symbol subtest: The survivor (high-dose chemotherapy) group scored significantly lower than the control group ($p = 0.017$). No differences were found between the survivor (high-dose chemotherapy) and survivor (standard-dose chemotherapy) or survivor (standard-dose chemotherapy) and control group. **Language:** Dutch Aphasia Society Test word fluency subtest: No difference was found among the three groups. **Motor function:** Fepsy fingertapping (dominant): The survivor (high-dose chemotherapy) group scored significantly lower than the control group ($p = 0.041$). No difference was found between the survivor (high-dose chemotherapy) and survivor (standard-dose chemotherapy) or survivor (standard-dose chemotherapy) and controls. Fepsy fingertapping (nondominant): The survivor (high-dose chemotherapy) group scored significantly lower than the control group ($p = 0.004$). No difference was found between the survivor (high-dose chemotherapy) and survivor (standard-dose chemotherapy) or survivor (standard-dose chemotherapy) and controls. **Visuospatial skill:** RCFT copy: No differences were found among the three groups. **Verbal memory:** RAVLT: No differences were found among the three groups for recall, delayed recall, or recognition. **Visual memory:** RCFT recall: The survivor (high-dose chemotherapy) group scored significantly lower than the control group ($p = 0.028$). No differences were found between the survivor (high-dose chemotherapy) and survivor (standard-dose chemotherapy) groups or survivor (standard-dose chemotherapy) and control groups.	• Significant differences existed among the two survivor groups and the control group in relation to menopausal status. • The study accounted for anxiety and depression, but fatigue was not measured.

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AC—doxorubicin and cyclophosphamide; CAF—cyclophosphamide, doxorubicin, and 5-fluorouracil; CCC—cyclophosphamide, cisplatin, and carmustine; CEF—cyclophosphamide, epirubicin, and 5-fluorouracil; CMF—cyclophosphamide, methotrexate, and 5-fluorouracil; COWA—controlled oral word association; CTC—cyclophosphamide, thiotepa, and carboplatin; CVLT—California Verbal Learning Test; FEC—5-fluorouracil, epidoxorubicin, and cyclophosphamide; HRNB—Halstead-Reitan Neuropsychological Test Battery; HSCS—High Sensitivity Cognitive Screen; MAE—Multilingual Aphasia Examination; N/A—not applicable; PASAT—Paced Auditory Serial Addition Test; RAVLT—Rey Auditory Verbal Learning Test; RBANS—Repeatable Battery for the Assessment of Neuropsychological Status; RCFT—Rey Complex Figure Test; TMT—Trail Making Test; WAIS—Wechsler Adult Intelligence Scale; WMS—Wechsler Memory Scale

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Table 1. Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer *(Continued)*

Study	Sample Characteristics	Findings	Limitations
Wefel et al., 2004 **Purpose:** to evaluate the incidence, nature, severity, and chronicity of cognitive dysfunction among patients with breast carcinoma who are treated with a standard dose of adjuvant chemotherapy **Design:** prospective study of survivors	• N = 18 • Mean age = 45.4 ± 6.7 years • Mean educational level = 14 ± 2.6 years • Mean time since treatment = N/A at baseline, three weeks, and one year • Chemotherapy regimens: CAF • One-third of participants were postmenopausal.	**Attention/concentration:** WAIS digit span subtest: No differences were found among the three time periods. WAIS arithmetic subtest: No differences were found among the three time periods. **Executive function:** Category Booklet Test: Patients had significantly higher scores (indicating decreased executive function) three weeks postchemotherapy compared to baseline ($p < 0.01$). No differences were found between one year after chemotherapy compared to baseline. HRNB TMT Part B: No differences were found among the three time periods. WAIS similarities subtest: No differences were found among the three time periods. **Information processing speed:** HRNB TMT Part A: No differences were found among the three groups or the three time periods. WAIS digit symbol subtest: Patients had significantly higher scores (indicating decreased speed of information processing) at short-term (three weeks) postchemotherapy compared to baseline ($p < 0.05$). No differences were found between long-term (one year) postchemotherapy compared to baseline. **Language:** Not measured **Motor function:** Grooved pegboard (dominant): No differences were found among the three time periods. Grooved pegboard (nondominant): No differences were found among the three time periods. **Visuospatial skill:** WAIS block design subtest: Patients had significantly higher scores (indicating decreased visuospatial skill) at short-term (three weeks) postchemotherapy compared to baseline ($p < 0.05$). No difference was found between long-term (one year) postchemotherapy compared to baseline. **Verbal memory:** Buschke verbal selective reminding test: long-term storage and delayed recall. Patients had significantly lower scores at short-term (three weeks) postchemotherapy compared to baseline ($p < 0.05$). No differences were found between long-term (one year) postchemotherapy compared to baseline. **Visual memory:** Buschke nonverbal selective reminding test: long-term storage and delayed recall. Patients had significantly lower scores at short-term (three weeks) postchemotherapy compared to baseline ($p < 0.05$). No differences were found between long-term (one year) postchemotherapy compared to baseline.	• Small sample size • Significant attrition • The study accounted for depression and anxiety, but fatigue was not measured.
Wieneke & Dienst, 1995 **Purpose:** to determine whether objective evidence exists for deterioration in cognitive function and whether further large-sample, prospective research is warranted. **Design:** retrospective study of survivors	• N = 28 • Mean age = 42 ± 6.7 years • Mean educational level = 16 ± 2.1 years • Mean time since treatment = 6.6 months • Chemotherapy regimens: 61% CMF, 14% CAF, 25% combination of both • Average course of therapy = 6.7 months • 39% were on tamoxifen. • 11% of survivors had evidence of depression.	**Attention/concentration:** WAIS digit span subtest: Survivors had significantly lower scores compared to test norms ($p = 0.007$). **Executive function:** Category Booklet Test: No difference was found. HRNB TMT Part B: No difference was found. WAIS similarities subtest: No difference was found. **Information processing speed:** HRNB TMT Part A: Survivors had significantly higher scores (indicating decreased information processing speed) compared to norms ($p < 0.011$). PASAT: Survivors had significantly lower scores than test norms ($p < 0.003$). WAIS digit symbol subtest: No difference was found. **Language:** MAE COWA: Survivors had significantly lower scores than test norms ($p = 0.017$). **Motor function:** Grooved pegboard (dominant): Survivors had significantly lower scores than test norms ($p < 0.001$). Grooved pegboard (nondominant): Survivors had significantly lower scores than test norms ($p < 0.025$). **Visuospatial Skill:** RCFT copy: Survivors had significantly lower	• Small sample size, especially for multiple chemotherapy regimens, variable duration of regimens, and variability in time since last treatment • No information regarding menopausal status • Accounted for depression, but anxiety and fatigue were not measured.

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AC—doxorubicin and cyclophosphamide; CAF—cyclophosphamide, doxorubicin, and 5-fluorouracil; CCC—cyclophosphamide, cisplatin, and carmustine; CEF—cyclophosphamide, epirubicin, and 5-fluorouracil; CMF—cyclophosphamide, methotrexate, and 5-fluorouracil; COWA—controlled oral word association; CTC—cyclophosphamide, thiotepa, and carboplatin; CVLT—California Verbal Learning Test; FEC—5-fluorouracil, epidoxorubicin, and cyclophosphamide; HRNB—Halstead-Reitan Neuropsychological Test Battery; HSCS—High Sensitivity Cognitive Screen; MAE—Multilingual Aphasia Examination; N/A—not applicable; PASAT—Paced Auditory Serial Addition Test; RAVLT—Rey Auditory Verbal Learning Test; RBANS—Repeatable Battery for the Assessment of Neuropsychological Status; RCFT—Rey Complex Figure Test; TMT—Trail Making Test; WAIS—Wechsler Adult Intelligence Scale; WMS—Wechsler Memory Scale

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Table 1. Studies of Chemotherapy-Induced Cognitive Impairments in Women With Breast Cancer *(Continued)*

Study	Sample Characteristics	Findings	Limitations
		scores compared to norms ($p < 0.0001$). WAIS block design subtest: No difference was found. **Verbal memory:** CVLT: No difference was found. CVLT short delay: No difference was found. CVLT long delay: Survivors had significantly lower scores compared to test norms ($p = 0.049$). **Visual memory:** RCFT recall: Survivors had significantly lower scores than test norms ($p < 0.001$).	

AC—doxorubicin and cyclophosphamide; CAF—cyclophosphamide, doxorubicin, and 5-fluorouracil; CCC—cyclophosphamide, cisplatin, and carmustine; CEF—cyclophosphamide, epirubicin, and 5-fluorouracil; CMF—cyclophosphamide, methotrexate, and 5-fluorouracil; COWA—controlled oral word association; CTC—cyclophosphamide, thiotepa, and carboplatin; CVLT—California Verbal Learning Test; FEC—5-fluorouracil, epidoxorubicin, and cyclophosphamide; HRNB—Halstead-Reitan Neuropsychological Test Battery; HSCS—High Sensitivity Cognitive Screen; MAE—Multilingual Aphasia Examination; N/A—not applicable; PASAT—Paced Auditory Serial Addition Test; RAVLT—Rey Auditory Verbal Learning Test; RBANS—Repeatable Battery for the Assessment of Neuropsychological Status; RCFT—Rey Complex Figure Test; TMT—Trail Making Test; WAIS—Wechsler Adult Intelligence Scale; WMS—Wechsler Memory Scale

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categories test revealed significant deficits in the longitudinal study (Wefel et al.), it did not find deficits in the cross-sectional studies (Freeman & Broshek; Wieneke & Dienst).

Information Processing Speed

Information processing speed refers to the brain's ability to rapidly process simple and complex information (Freeman & Broshek, 2002). Because the input of information may be tactile, auditory, verbal, or visual, this domain is inter-related with all of the other domains of cognitive function and may have a direct influence on the ability to store such information into memory.

Seven studies used neuropsychological tests to measure information processing speed, but only six of the studies reported their findings. Of note, the findings regarding chemotherapy-induced impairment in processing speed are inconsistent. Five studies found significant deficits in information processing speed (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995; Wefel et al., 2004), whereas one found no difference (Freeman & Broshek, 2002). All of the studies that found significant deficits were conducted with survivors. In one study, significant impairment in information processing speed was found for high-dose but not standard-dose chemotherapy (van Dam et al.).

Tests that found significant differences included the Paced Auditory Serial Addition Test, Digit Symbol, Trail Making Test-Part A, and Fepsy visual reaction (versus the Fepsy binary choice and Fepsy visual searching, which did not). In four studies (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998; Wefel et al., 2004), the digit symbol test demonstrated significant deficits but not in another study (Wieneke & Dienst, 1995). Two possible explanations for these differences are the length of time since the administration of chemotherapy or differences in the comparison groups. Studies that found significant impairments had survivors who had been off treatment 2–10 years compared to the control group (Ahles et al., 2002; Schagen et al., 1999; van Dam et al.) or survivors who had been off treatment for three weeks compared to patients' own baselines (Wefel et al.). The study that did not find deficits compared the test scores of survivors who had been off chemotherapy for only six months with normative scores for the various neuropsychological tests.

Language

Language incorporates oral and written communication when used to express thoughts. Impairment in language inhibits the ability to communicate with others and follow directions without needing repetitions and explanations. Language processing involves representing, comprehending, and communicating symbolic information, either written or spoken (Gazzaniga et al., 2002).

All of the studies used neuropsychological tests to measure language, but only eight reported their findings. Again, the findings regarding chemotherapy-induced impairment in language are inconsistent. Four studies found significant deficits in language (Brezden et al., 2000; Schagen et al., 1999; Tchen et al., 2003; Wieneke & Dienst, 1995), whereas four found no differences (Ahles et al., 2002; Freeman & Broshek, 2002; van Dam et al., 1998; Wefel et al., 2004). All of the studies that found significant deficits were conducted with survivors, with the exception of one study (Brezden et al.).

Tests that yielded significant differences included word fluency tests and the language subtest of the HSCS. The Boston Naming Test, vocabulary and reading subtests of the Wide Range Achievement Test, and language subtest of the RBANS did not find deficits. Word fluency tests revealed significant deficits in all but one study of survivors (van Dam et al., 1998). A potential explanation for these differences may be the heterogeneity of chemotherapy regimens that the survivors received.

Motor Function

Motor function relates to motor performance, such as speed, strength, and coordination. All of the studies used neuropsychological tests to measure motor function, but only eight reported their findings. Once again, the findings regarding chemotherapy-induced impairment in motor function are inconsistent. Five studies found significant deficits in motor function (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995), but three found no differences (Freeman & Broshek, 2002;

Tchen et al., 2003; Wefel et al., 2004). All of the studies that found significant deficits were performed in survivors. In one of those studies, significant impairment in motor function was found with high-dose but not for standard-dose chemotherapy (van Dam et al.). All of the tests used (i.e., grooved pegboard, fingertapping, thumb-finger sequencing, and the visual-motor subtest of the HSCS) yielded significant differences.

Visuospatial Skill

Visuospatial skill refers to the ability to process and interpret visual information regarding where things are situated in space (Spreen & Strauss, 1998). Although all of the studies used neuropsychological tests to measure visuospatial skill, only eight reported their findings. Of note, the findings regarding chemotherapy-induced impairment in visuospatial skill are inconsistent. Only three studies found significant deficits in visuospatial skill (Freeman & Broshek, 2002; Wefel et al., 2004; Wieneke & Dienst, 1995), whereas five found no differences (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998). One possible explanation for the inconsistent findings is the various comparison groups. Studies that found significant deficits compared survivors with patients who currently were receiving chemotherapy (Freeman & Broshek), with baseline scores (Wefel et al.), or with normative scores for the various neuropsychological tests (Wieneke & Dienst). In contrast, studies that did not find deficits compared survivors with a control group (Ahles et al., 2002; Brezden et al.; Schagen et al., 1999; Tchen et al.; van Dam et al.).

The tests that yielded significant differences were the complex figure copy, block design, and the visual-construction subtest of the RBANS. The spatial subtest of the HSCS did not reveal any deficits. Although the complex figure copy was used in three studies, significant deficits were found in only one study (Wieneke & Dienst, 1995). In contrast to the other studies, survivors in the Wieneke and Dienst study were only six months from treatment (versus approximately two years), and results were compared to normative data rather than to a control group. Similarly, the block design also was used in three studies, but significant deficits were found in only the longitudinal study (Wefel et al., 2004).

Memory

Memory is an outcome of learning that is created and strengthened by repetition (Gazzaniga et al., 2002). Memory infers the ability to acquire, store, and use new information (Grober, 2002). The most common types of memory are visual and verbal. Although all of the studies used neuropsychological tests to measure verbal memory, only eight reported their findings. Again, the findings regarding chemotherapy-induced impairment in verbal memory are inconsistent. Four studies found significant deficits in verbal memory (Brezden et al., 2000; Schagen et al., 1999; Wefel et al., 2004; Wieneke & Dienst, 1995), but four found no differences (Ahles et al., 2002; Freeman & Broshek, 2002; Tchen et al., 2003; van Dam et al., 1998). Deficits were found in survivors and patients receiving chemotherapy.

Tests that revealed significant deficits were the California Verbal Learning Test (CVLT), Rey Auditory Verbal Learning Test (RAVLT), Verbal Selective Reminding Test, and the memory subtest on the HSCS. However, the tests detected deficits in only half of the studies in which they were used. For example, the CVLT revealed significant deficits in survivors who were six months from treatment (Wieneke & Dienst, 1995) but did not show deficits in survivors who had been treated approximately 10 years prior (Ahles et al., 2002). A possible explanation for the differences with the RAVLT may be the differences in chemotherapy regimens. Patients in the study that found significant deficits with the RAVLT had received cyclophosphamide, methotrexate, and 5-fluorouracil (Schagen et al., 1999) versus 5-fluorouracil, epirubicin, and cyclophosphamide with or without cyclophosphamide, thiotepa, and carboplatin in the study that did not find deficits (van Dam et al., 1998). A potential explanation for the difference in test results with the memory subtest of the HSCS is not forthcoming. Deficits were not found with the logical memory test, memory subtest of the RBANS, and Hopkins Verbal Learning Test.

Although seven studies used neuropsychological tests to measure visual memory, only six of them reported their findings. Of note, the findings regarding chemotherapy-induced impairment in visual memory are inconsistent. Four studies found significant deficits in visual memory (Schagen et al., 1999; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995), whereas two studies found no differences (Ahles et al., 2002; Freeman & Broshek, 2002). All of the studies that found significant deficits were conducted with survivors. In one of those studies, impairment in visual memory was found with high-dose but not standard-dose chemotherapy (van Dam et al.). The complex figure recall, nonverbal Selective Reminding Test, and Wechsler Memory Scale recall instruments revealed significant deficits. The only study of survivors that did not find deficits in visual memory consisted of an older sample of survivors who had been treated 10 years prior and used the visual reproduction test (Ahles et al., 2002).

Summary

This review of studies that evaluated chemotherapy-induced impairments in cognitive function in women with breast cancer provides some insights into the specific cognitive domains that are affected by chemotherapy. Table 2 summarizes the findings from all of the studies. In the study of survivors, impairments in speed of information processing and motor function were identified most frequently. The limited number of studies of patients who received concurrent chemotherapy does not permit definitive conclusions to be drawn on the effects of chemotherapy on various domains of cognitive function.

Only nine studies were found that evaluated chemotherapy-induced deficits in cognitive function in women with breast cancer, with a total sample size of 720. Because only eight studies reported detailed findings (i.e., means and standard deviations), the sample size available for this critique was 617. Only 139 of these women with breast cancer currently were receiving chemotherapy. Of the 239 breast cancer survivors who had received chemotherapy, 205 had received standard-dose chemotherapy and 34 had received high-dose chemotherapy. The remaining 239 women were from the control groups.

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Table 2. Chemotherapy-Induced Cognitive Impairments Found in Studies of Women With Breast Cancer

Author(s)	Attention	Executive Function	Speed of Information Processing	Language	Motor Function	Visuospatial Skill	Verbal Memory	Visual Memory
Studies of survivors								
Ahles et al., 2002	–	N/A	X	–	X	–	–	–
Brezden et al., 2000	–	–	N/A	X	X	–	–	N/A
Freeman & Broshek, 2002	–	X	–	–	–	–	–	–
Schagen et al., 1999	X	X	X	X	X	–	X	X
Schagen et al., 2002[a]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
van Dam et al., 1998	X	–	X	–	X	–	–	X
Wefel et al., 2004	–	X	X	N/A	–	X	X	X
Wieneke & Dienst, 1995	X	–	X	X	X	X	X	X
Studies of patients currently receiving chemotherapy								
Brezden et al., 2000	–	–	N/A	X	–	–	X	N/A
Freeman & Broshek, 2002	–	–	–	–	–	X	–	–
Tchen et al., 2003	–	–	N/A	X	–	–	–	N/A

[a] All of the domains were assessed, but detailed findings were not reported.

Note. N/A indicates not assessed, X indicates significant impairment, and – indicates no significant impairment.

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The control groups consisted of 103 patients with breast cancer who had received only local therapy (i.e., surgery or RT) and 136 healthy women. Individual study sample sizes ranged from 18–200, with 18–100 patients receiving chemotherapy or survivors. Although only one study reported a power calculation (Tchen et al., 2003), it was not the only study to find chemotherapy-induced deficits in various domains of cognitive function.

Of the studies that reported findings, at least half found significant chemotherapy-induced impairments in breast cancer survivors in speed of information processing (83%), motor function (71%), visual memory (67%), and language (50%). Deficits in attention and concentration (43%), executive function (43%), verbal memory (43%), and visuospatial skill (29%) were not found as frequently.

In the one longitudinal study (Wefel et al., 2004), significant deficits were found three weeks after completion of chemotherapy in five of the seven domains that were assessed. Wieneke and Dienst's (1995) study, which evaluated patients approximately six months after chemotherapy, found significant deficits in seven of the eight cognitive domains assessed. In the three studies that evaluated women about two years after chemotherapy, results were inconsistent, with cognitive deficits found in two of the six (Brezden et al., 2000), four of the eight (van Dam et al., 1998), and seven of the eight (Schagen et al., 1999) domains assessed. One study that evaluated patients almost 10 years after chemotherapy (Ahles et al., 2002) found deficits in only two of the seven domains assessed, information processing speed and motor function. Although chemotherapy-induced deficits are believed to decrease over time, additional research is needed to confirm this hypothesis.

Findings regarding cognitive deficits in women with breast cancer who currently were receiving chemotherapy were even less clear. Of the three prospective studies, one involved a pilot study with only 17 women (Freeman & Broshek, 2002). Because Freeman and Broshek's findings were compared with data from survivors who had received chemotherapy, rather than a control group or normative data, accurately interpreting the results is difficult.

The two remaining studies (Brezden et al., 2000; Tchen et al., 2003) used the HSCS to measure six of the eight cognitive domains (i.e., attention and concentration, executive function, language, motor function, visuospatial skill, and verbal memory). Although the pilot study (Brezden et al.) found significant deficits in language and verbal memory, the subsequent study (Tchen et al.) found significant deficits in language only. The HSCS was not used in any of the retrospective studies or the other prospective study (Freeman & Broshek, 2002). Therefore, whether this test is not sensitive enough to detect deficits in women with breast cancer currently receiving chemotherapy, or whether the deficits are more pronounced after chemotherapy is completed, is unclear.

Two studies (Brezden et al., 2000; Tchen et al., 2003) used the subtests of one test, the HSCS, to evaluate each cognitive domain, whereas the other seven studies (Ahles et al., 2002; Freeman & Broshek, 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995) used one to five different tests to evaluate each cognitive domain. Therefore, determining whether the variable findings, which resulted from the 40 tests or subtests that were used to measure the eight cognitive domains, were a result of a lack of deficits or the fact that some of the instruments were not sensitive enough to detect chemotherapy-induced impairments is difficult. Despite these findings, the results reveal a number of conceptual and methodologic issues that should be addressed in future studies.

Conceptual Issues

The lack of a conceptual definition of cognitive function and its corresponding domains was identified as a problem in this review. Only Freeman and Broshek (2002) defined the cognitive domains that were measured. Although all of the studies referenced their tests by cognitive domains, the number of domains identified was inconsistent. Half of the studies identified seven cognitive domains (Ahles et al., 2002;

Schagen et al., 1999, 2002; van Dam et al., 1998; Wefel et al., 2004), but three acknowledged only six domains (Brezden et al., 2000; Freeman & Broshek, 2002; Tchen et al., 2003), and one (Wieneke and Dienst, 1995) included depression, for a total of nine domains. In addition, in some studies the domains were not specified clearly. For example, Ahles et al. (2002) separated verbal and visual memory into two distinct domains, but others did not (Freeman & Broshek; Schagen et al., 1999, 2002; van Dam et al.; Wefel et al.; Wienke & Dienst).

Other differences in distinguishing cognitive domains are not as obvious, and some of the confusion may be a function of their interdependence. Certain cognitive domains are so inextricably linked that impairment in one domain invariably affects another (Lezak et al., 2004). Additionally, some neuropsychological tests (e.g., Digit symbol, Trail Making Test-Parts A and B, word fluency) may measure aspects of more than one domain, which makes assignment of the findings to a specific domain or multiple domains inconsistent over studies.

Methodologic Issues

Forty-three different tests and subtests were used by the various studies in this review, and each test was assigned to a single domain as listed in Table 3. The number of tests used to assess any specific domain of cognitive function ranged from one to five. With the exception of the HSCS, the investigators did not provide details on the reliability and validity of the tests used. Therefore, the findings from the studies are difficult to compare and interpret because of the lack of information about the psychometric strengths of the tests specific to the measurement of cognitive function.

Implementing procedures to ensure that each investigator performs reliable and valid coding of an instrument is important (Lezak et al., 2004). Adequate training may be required to accurately administer and score tests, because even the slightest deviations from standard procedures and inconsistencies in administration can affect the validity of test results (Hebben & Milberg, 2002). Although the scoring of the instruments used was consistent with standardized procedures, information regarding the training of those responsible for the testing (including the number of people involved) was available in only one study (Ahles et al., 2002).

Many valid and reliable instruments are available to assess cognitive function. Selection of the most appropriate instrument depends on the research questions, characteristics of the patient population, and specific domains to be measured. A single instrument (or a battery of instruments) may be used to measure each cognitive domain. Most studies used a lengthy battery of tests, which took from two to three hours to administer (Ahles et al., 2002; Freeman & Broshek, 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995). Participant burden is an important consideration in the development of future studies of chemotherapy-induced impairment in cognitive function in patients with cancer. Patients who currently are receiving chemotherapy may be experiencing other side effects that may limit their ability or willingness to complete lengthy evaluations.

Education level and intelligence have strong, positive relationships with neuropsychological test performance and have been found to be protective against cognitive impairments associated with brain trauma (Lezak et al., 2004). Additionally, cognitive decline occurs with aging. All but one (Freeman & Broshek, 2002) of the studies in this review stated that they

Table 3. Neuropsychological Tests Used to Assess Chemotherapy-Induced Impairments by Cognitive Domain

Cognitive Domain	Tests Used
Attention and concentration	• Continuous Performance Test: distractibility and vigilance subtests • D2 Test • High Sensitivity Cognitive Screen (HSCS): attention subtest • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): attention subtest • Wechsler Adult Intelligence Scale (WAIS): arithmetic and digit span subtests
Executive function	• Booklet Category Test • HSCS: self-regulation and planning subtest • Halstead-Reitan Neuropsychological Test Battery (HRNB): categories test and Trail Making Test (TMT)-Part B subtests • Stroop test • WAIS: similarities subtest
Speed of information processing	• Fepsy: binary choice, visual reaction, and visual searching subtests • HRNB: TMT Part A subtest • Paced Auditory Serial Addition Test • WAIS: digit symbol subtest
Language	• Boston Naming Test • Dutch Adult Reading Test • Dutch Aphasia Society Test: word fluency subtest • Groninger Intelligence Test: word fluency subtest • HSCS: language subtest • Multilingual Aphasia Examination: controlled oral word association subtest • RBANS: language subtest • S.A.N.: word fluency subtest • WAIS: vocabulary subtest • Wide Range Achievement Test: reading subtest
Motor function	• Fepsy: fingertapping subtest • Grooved pegboard • HSCS: visual motor subtest • HRNB: fingertapping subtest • Thumb-finger sequencing
Visuospatial skill	• Rey Complex Figure Test (RCFT): copy • HSCS: spatial subtest • RBANS: visual construction subtest • WAIS: block design subtest
Verbal memory	• Buschke Verbal Selective Reminding Task • California Verbal Learning Test • HSCS: memory subtest • Hopkins Verbal Learning Test • RBANS: memory subtest • Rey Auditory Verbal Learning Test • Wechsler Memory Scale (WMS): logical memory subscale
Visual memory	• Buschke Nonverbal Selective Reminding Test • RCFT: recall • WMS: Facial recognition and visual reproduction subtests

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controlled for age and educational level, but most of the neuropsychological tests have normative data based on age and gender. These data were not used for comparative purposes in most of the studies.

Of the seven studies that used a control group, five matched women in the control group with those in the chemotherapy group by age (Ahles et al., 2002; Schagen et al., 1999, 2002; Tchen et al., 2003; van Dam et al., 1998), whereas one did not (Brezden et al., 2000). Other potential confounding covariates, such as depression, anxiety, fatigue, and hormonal status, were not measured as consistently.

The influence of decreased sex steroid hormones such as estrogen on cognitive function has been implicated in deficits in learning and memory, especially verbal memory (Cutter, Norbury, & Murphy, 2003; Erlanger, Kutner, Jacobs, 1999; O'Shaughnessy, 2003; Sherwin, 1996, 1998). Chemotherapy is known to affect ovarian function, leading to temporary or permanent amenorrhea in women, especially in those older than 40 (Aikin, 1995; Knobf, 1998; Padmanabhan, Wang, Moore, & Rubens, 1987). Only one study controlled for menopausal status in the analysis (Brezden et al., 2000). However, the authors did not state whether that factor influenced their findings. Tchen et al. (2003) measured menopausal symptoms but did not find any association with cognitive deficits.

Eight of the nine studies in this review measured depression. Although two found a significant inverse relationship with cognitive deficits, as measured by the Center for Epidemiological Studies Depression Inventory (CES-D) or the Hopkins Symptom Checklist (Freeman & Broshek, 2002; Schagen et al., 2002), five studies did not find any correlations between cognitive deficits and depression, as measured by the CES-D, Hopkins Symptom Checklist, Minnesota Multiphasic Personality Inventory (MMPI) depression scale, or the Beck Depression Inventory (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995). One study (Brezden et al., 2000) assumed that a correlation between depression and cognitive deficits did not exist because no differences existed in mood disturbances, as measured by the Profile of Mood States (POMS), between the chemotherapy and control groups.

Six of the nine studies measured anxiety. Five of the studies did not find significant correlations between cognitive deficits and anxiety as measured by the State-Trait Anxiety Inventory, Hopkins Symptom Checklist, or the anxiety scale of the MMPI (Ahles et al., 2002; Schagen et al., 1999, 2002; van Dam et al., 1998; Wefel et al., 2004). All of the studies that did not find a relationship between anxiety and cognitive deficits were performed in survivors. The one prospective study (Brezden et al., 2000) did not examine the relationship between anxiety and cognitive deficits, because no differences were found in mood disturbances, as measured by POMS, between the chemotherapy and control groups. Similarly, in the five studies that measured fatigue with the Fatigue Symptom Inventory, European Organization for Research and Treatment-Quality of Life Cancer-30 questionnaire, or the Functional Assessment of Cancer Therapy-Fatigue, none found a significant correlation with cognitive deficits (Ahles et al., 2002; Schagen et al., 1999, 2002; Tchen et al., 2003; van Dam et al.).

Although anxiety, depression, and fatigue can reduce performance on neuropsychological tests, one reason for the absence of correlations in studies of survivors may be the length of time since treatment. The experience of fatigue and psychological factors, such as depression and anxiety, may be different in survivors compared to patients who currently are receiving chemotherapy. Another potential explanation for the lack of correlations might be the choice of the comparison group. Patients with breast cancer who received local therapy may share some emotional and physical concerns with those who receive chemotherapy. Overall, differences in psychological and physical status of survivors compared to women who currently are receiving chemotherapy, along with the small number of available studies, suggest the need for further investigation of these potential covariates.

Another potential risk factor not included in any of the aforementioned studies is the presence of the apolipoprotien E (APOE) ε4 gene, which has been associated with decreased cognitive function in aged individuals (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Yaffe, Cauley, Sands, & Browner, 1997). One preliminary study of cancer survivors found a greater risk for deficits in visual memory and visuospatial skills in those who had at least one ε4 allele of APOE (Ahles et al., 2003).

Interpretation of these findings is complicated further by the cross-sectional design used by eight of the studies reviewed. Because only one study (Wefel et al., 2004) had information regarding the baseline cognitive function of patients, readers cannot determine whether patients had worsening, stable, or improved cognitive functioning after the initiation and completion of treatment. Longitudinal studies need to be performed to determine when chemotherapy-induced deficits in cognitive function occur, which domains of cognitive function are affected, and whether different domains are affected at different times after the administration of chemotherapy.

All of the studies used a convenience sample. Although this approach is the most common method to obtain participants, the ability to obtain a representative sample often is a problem (Polit & Hungler, 1999). All of the studies reviewed have the potential for selection bias. For example, the studies that included survivors required patients to be free of disease or other medical complications, which excluded sicker patients with potentially more cognitive deficits. In addition, whether patients who declined to participate had greater cognitive deficits is unknown.

Only one study failed to describe its inclusion and exclusion criteria (Freeman & Broshek, 2002). Although the remaining eight studies provided explicit information regarding sample selection, only seven provided response rates, which ranged from 70%–80% (Ahles et al., 2002; Schagen et al., 1999, 2002; Tchen et al., 2003; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995). In two of the studies (Tchen et al.; Wieneke & Dienst), participants were recruited from more than one site. Of the two prospective studies that used healthy women as a control group, one matched for age (Tchen et al.), but the other did not (Brezden et al., 2000). The remaining prospective study compared women currently receiving chemotherapy to survivors (Freeman & Broshek).

Only one retrospective study did not have a control group (Wieneke & Dienst, 1995). The control groups in the other studies of survivors consisted of women who had received only local treatment and were matched for age with the chemotherapy survivors (Ahles et al., 2002; Schagen et al., 1999, 2002; van Dam et al., 1998). In two of the studies, no statistically significant differences were found between the individual neuropsychological test scores of the patients in the control group and the published norms for those tests (Schagen et al., 1999; van Dam et al.).

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Suggestions for Future Research

Although research is beginning to elucidate the presence of cognitive impairments in survivors, the limited number of published studies is beset with multiple methodologic and conceptual issues. The paucity of scientific knowledge is even more pronounced for patients with breast cancer who currently are receiving chemotherapy. The use of conceptual models or theoretical frameworks would aid future research and help identify variables that explain or predict the relationships among chemotherapy, clinical and patient characteristics, and cognitive impairments. In addition, the incorporation of qualitative research methodologies would enhance the understanding of the complexity of patients' experiences with cognitive impairments.

Further investigation is needed to identify the tests that are most valid, reliable, sensitive, and specific for detecting short-term and persistent chemotherapy-induced cognitive impairments. Researchers of future studies may want to use the instruments that consistently distinguish deficits, such as the digit span for attention and concentration; digit symbol, Fepsy visual reaction, and Trail Making Test-Part A for information processing speed; word fluency for language; fingertapping or grooved pegboard for motor function; and complex figure copy and recall for visuospatial skill and visual memory. Although instruments that have demonstrated an ability to detect deficits should be used, multiple measures may be preferable for the domains for which measures that possess sufficient sensitivity or specificity have not been identified. Regardless of which tests are chosen, participant burden is an important consideration.

The published findings suggest that chemotherapy-induced impairments in cognitive function do occur in some women with breast cancer, but differences in time since treatment, chemotherapy regimen, menopausal status, and tests used have limited comparisons among the various studies. Therefore, ascertaining whether deficits were associated with a particular drug in a chemotherapy regimen, with chemotherapy-induced menopause, or even with the use of tamoxifen is difficult. Further studies are necessary to understand potential cognitive deficits induced by chemotherapy, but the conceptual and methodologic problems identified in this review also must be addressed.

Implications for Nursing

Impairments in cognitive function adversely affect the immediate treatment experience and a return to normal life after treatment is completed. The immediate complications of such cognitive dysfunction also may impair the ability of patients to give informed consent, identify treatment toxicities, learn self-care measures, and perform self-care behaviors. Increasing awareness among cancer survivors and healthcare professionals regarding such negative impacts of chemotherapy has given rise to a growing number of important studies and further emphasizes the need to understand the influence of chemotherapy on cognitive function.

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