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**FACULTY OF GRADUATE AND
POSTDOCTORAL STUDIES**

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**An Examination of Chemo Fog: Cognitive Decline in Early-stage Breast Cancer Patients Treated with
Adjuvant Chemotherapy**

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**An examination of chemo fog: cognitive decline in early-stage
breast cancer patients treated with adjuvant chemotherapy**

Angela Stewart

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ABSTRACT

There is a growing concern that women diagnosed with breast cancer may be susceptible to neuropsychological deficits secondary to adjuvant chemotherapy. Commonly referred to as chemofog, this phenomenon has been associated with neuropsychological decline in many areas of cognitive functioning. To consolidate the findings from several small, previously published studies, the first objective of this thesis was to use meta-analytic techniques to estimate the magnitude of neuropsychological deficits among breast cancer patients exposed to adjuvant chemotherapy. Results showed that neuropsychological test scores were approximately one-quarter to one-half a standard deviation below comparison levels on most cognitive domains.

The second phase of this thesis involved a prospective investigation of the short-term neuropsychological effects of adjuvant chemotherapy among a cohort of early stage breast cancer patients treated with adjuvant chemotherapy, hormonal therapy alone, and a group of non-cancer, healthy controls. All participants received baseline assessment of neuropsychological and psychological functioning prior to the start of adjuvant chemotherapy (where applicable). All tests and questionnaires were re-administered following completion of the last cycle of chemotherapy, or at an equivalent time point in the hormonal or healthy control groups.

Results revealed a modest but significantly greater risk of cognitive decline in the chemotherapy group (26%) relative to the hormonal participants (8%). Patients exposed to chemotherapy were 3.3 times more likely to experience reliable cognitive decline compared to hormonal participants. However, when change scores for both the hormonal and chemotherapy groups were referenced to a small sample of healthy control participants, the difference in frequency of cognitive decline between the treatment groups (chemotherapy

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LEGEND

Analysis of variance	ANOVA
Arimidex, Tamoxifen alone, or in combination	ATAC
Beck Depression Inventory	BDI
Beck Depression Inventory-II	BDI-II
Blood brain barrier	BBB
Confidence interval	CI
Cyclophosphamide	C
Doxorubicin	A
Electroencephalography	EEG
Epirubicin	E
Estrogen-receptor negative	ER-
Estrogen-receptor positive	ER+
Event related potentials	ERP
Flourouracil	F
High Sensitivity Cognitive Screen	HSCS
Hormone replacement therapy	HRT
Intelligence quotient	IQ
Methotrexate	M
Multivariate analysis of variance	MANOVA
Profile of Mood States	POMS
Reliable change index	RCI
Standard deviation	SD
Standard error of the mean	SEM

Statistical Package for the Social Sciences	SPSS
Thiopeta	T
Tumor-node-metastasis	TNM
Wechsler Adult Intelligence Scale – Revised	WAIS-R
Wechsler Adult Intelligence Scale - Third edition	WAIS-III
Wechsler Memory Scale – third edition	WMS-III

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INTRODUCTION

Cancer is a common illness, with breast cancer in particular the most frequently diagnosed cancer among Canadian women. One in nine Canadian woman is expected to receive a diagnosis of breast cancer in her lifetime, and 1 in 25 is expected to die from this disease (National Cancer Institute, 2005a). This substantial increase in survivorship is the direct result of better screening and earlier detection coupled with improvements in treatment (National Cancer Institute, 2005b). This welcome consequence has led to a growing interest in quality of life issues, often related to identifying and minimizing the side effects associated with treatment for breast cancer.

Today, more and more women newly diagnosed with breast cancer undergo adjuvant treatment in the form of chemotherapy to prevent a recurrence (Harlan, Clegg, Abrams, Stevens, & Ballard-Barbash, 2006; Piccart et al., 2005). One particular area of active clinical and research interest is in the relationship between adjuvant chemotherapy treatment for breast cancer and neuropsychological function. Over the past decade, there has been a growing concern that women diagnosed with breast cancer may be susceptible to neuropsychological deficits secondary to adjuvant chemotherapy (Wefel, Kayl, & Meyers, 2004). Referred to as “chemofog” or “chemobrain” in the lay press, this phenomenon has been associated with neuropsychological decline in most areas of functioning, including attention/concentration, working memory, short- and long-term memory, speed of processing, language, spatial ability, and motor function (Ahles et al., 2002; Brezden, Phillips, Bunston, & Tannock, 2000; Castellon, Ganz, Bower, Petersen, Abraham, & Greendale, 2004; Schagen, van Dam, Muller, Boogerd, Lindeboom, & Bruning, 1999; van Dam et al., 1998; Wieneke & Dienst, 1995). While the majority of studies to date suggest that cognitive loss secondary to adjuvant chemotherapy is subtle in nature (e.g., Shilling,

Jenkins, Morris, Deutsch, & Bloomfield, 2005), frank cognitive impairment has also been reported (Brezden et al., 2000). Such cognitive decrements may translate into a delay in return to work, impact educational attainment, and more generally, reduce quality of life (Ahles & Saykin, 2001; Ahles & Saykin, 2002; Morse, Rodgers, Verrill, & Kendell, 2003).

While the evidence for chemotherapy-induced cognitive function is rising, the ability of a critical mass of published works to confidently establish a causal relationship has been hampered by problems with research design and poor control of potentially confounding factors. Many of the studies to date, while making a unique contribution, have lacked a pre-treatment or baseline neuropsychological assessment against which to gauge change as a function of treatment. Additionally, more than a dozen qualitative (narrative) reviews on the subject have been published in recent years, although until recently (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005), a quantitative analysis of these findings has been lacking.

Thus, this thesis has two goals. In an effort to consolidate the findings from several small, previously published papers, the first objective was to use meta-analytic techniques to estimate the magnitude of neuropsychological deficits among early stage breast cancer patients treated with adjuvant chemotherapy (Study 1). Using a prospective methodology, the second aim was designed to isolate the short-term neuropsychological effects of adjuvant chemotherapy among two groups of early stage breast cancer patients scheduled to receive adjuvant chemotherapy with or without hormonal therapy or hormonal therapy alone. A small group of non-cancer, healthy controls were also included to gauge the extent of practice effects associated with repeated, neuropsychological assessment (Study 2).

This thesis is organized into two papers that have been either published (Study 1) or submitted for publication (Study 2) to peer-reviewed journals. Before these are presented, there is a general introduction that describes background information and treatment of early stage breast cancer, critically reviews the existing literature associated with its treatment, and describes factors that influence performance on neuropsychological measures. The final section provides details of two studies that form this thesis. A general discussion is presented at the end of the thesis. Note that the terms neuropsychological decline and cognitive decline are used synonymously throughout this document.

Breast cancer

Background, risk factors, diagnosis

The structure of the female breast is complex. Each breast contains lobules of milk-producing glands that are surrounded by fat and connective tissue. Ducts serve to transport milk from these glands to the nipple. An important system of lymph vessels surrounds the breast and drains into lymph nodes located in the armpit.

Breast cancer refers to abnormal, unregulated cell growth. In some cases, the cancerous cells spread or metastasize to other regions of the body causing additional damage. The majority of breast cancers are slow growing.

The development of many breast cancers is promoted by estrogen, a female reproductive hormone. Breast cancer tumors that grow in response to estrogen, that is, are endocrine-dependent, are referred to as estrogen-receptor positive (ER+), while those that are not, are called estrogen-receptor negative (ER-). The most common type of breast cancer involves ER+ tumors (Early Breast Cancer Trialists' Collaborative Group, 2005).

Estrogen is directly produced by the ovaries as well as by other tissues in the body (e.g., adrenal glands, adipose/fat tissue) and brain. Estrogen levels fluctuate depending on the life cycle and are at their lowest during the menopausal period when the ovaries stop producing estrogen. Menopause is most likely to occur between the ages of 45 to 55 and is more specifically defined as the cessation of menses for 12 months in a row (National Cancer Institute, 2006). Following menopause, most circulating estrogen in the female body is due to a hormone called androgen that is produced by the adrenal glands. A protein in the muscle and fat tissue is responsible for producing an enzyme aromatase that changes androgen into estrogen. The ability to suppress estrogen production or block breast cancer cells from estrogen marks an important aspect of the treatment of this disease and is discussed in an upcoming section. The next section describes risks associated with the development of breast cancer and diagnostic issues, followed by a summary of treatments for early stage breast cancer that are most relevant to this thesis.

While there is no single cause of breast cancer, there are many different factors that are related to an increased risk. The two most important risk factors are gender and increasing age, both of which are unchangeable (National Cancer Institute, 2005b). Breast cancer is predominantly a female disease; male breast cancer accounts for less than 1% of all related diagnoses' (National Cancer Institute, 2005b). About 77% of breast cancers occur in women 50 years old and over and is most common among women 50 to 69 years old (Health Canada, 2003).

Other well-established biological risk factors of breast cancer include: (i) family history/genetic background, (ii) menarche before age 14, (iii) nulliparity, (iv) menopause after age 55, and (v) use of hormone replacement therapy (Daly, Bars Culver, Hull, & Levy-Lahad, 2003; Health Canada, 2003). Identified lifestyle risk factors include: (i)

obesity, (ii) poor diet, (iii) lack of physical exercise, (iv) alcohol consumption, (v) smoking, and (vi) use of birth control pills (Health Canada, 2003).

A significant component of breast cancer diagnosis involves determining whether the cancer has spread within the breast or elsewhere in the body. This is referred to as “staging” and is an important indicator of prognosis. The most common and internationally recognized staging classification is the tumor-node-metastasis (TNM) system that evaluates three key components: (1) the size of the primary tumor (T), (2) the extent of regional lymph node involvement (N), and (3) the presence or absence of metastases (M). TNM specifies five main staging categories (Stage 0, I, II, III, or IV) characterized by increasing disease severity (see Table 1; National Cancer Institute, 2005b; Singletary et al., 2002). The TNM system was updated in 2002 with changes to some nodal classifications such that some stage IIs are now classified as stage III (National Cancer Institute, 2005b; Singletary et al., 2002).

Treatment

Conventional treatment for early stage breast cancer is multimodal. Among early stage breast cancers, all visible and known cancerous tissue is removed surgically. However, given the slow-growth nature of most breast cancers, there may be undetected, micrometastatic disease present in the breast or other tissues that are not removed at the surgical site. Over the course of many years, this could develop into a life-threatening relapse (Early Breast Cancer Trialists’ Collaborative Group, 2005). Adjuvant systemic therapy is thus employed after surgery to reduce the likelihood of relapse by eliminating any unknown cancerous cells either in the breast or in other tissues. Treatment options in the adjuvant setting include chemotherapy, hormonal therapy, and radiation. Given that

Table 1. Staging criteria for early stage breast cancer.

Stage	Description*
0	- Carcinoma in situ (precancerous condition)
I	- Tumor is less than 2 cm with no lymph node involvement
IIA	- No tumor in breast but cancer in lymph nodes under the arm, or - Tumor is less than 2 cm and with positive underarm lymph nodes, or - Tumor is more than 2 cm but less than 5 cm with negative underarm lymph nodes
IIB	- Tumor is more than 2 cm but less than 5 cm with positive underarm lymph nodes, or - Tumor is greater than 5 cm with negative underarm lymph nodes
IIIA	- No tumor in breast but cancer in lymph nodes that have grown into each other or into other structures, or - Tumor is less than 5 cm with positive underarm lymph nodes that have grown into each other or into other structures, or - Tumor is greater than 5 cm and has positive underarm lymph nodes that may have grown into each other or other structures
IIIB	- Tumor can be any size and has spread to nearby tissue (e.g., chest wall) and may have spread to lymph nodes in breast or underarm
IIIC	- Tumor has spread to lymph nodes under collarbone and close to neck, or - Tumor may have spread to lymph nodes in breast or under the arm and to tissues near breast
IV	- Tumor has spread to other organs of the body

Note. cm = centimeters. * = National Cancer Institute (2005b); Singletary et al. (2002).

neuropsychological deficits have been attributed to both adjuvant chemotherapy and adjuvant hormonal treatment (Bender et al., 2006), each is discussed below. Not surprisingly, the iatrogenic effect of these treatments on neuropsychological function is the primary focus of Study 2.

Adjuvant chemotherapy. Adjuvant chemotherapy refers to chemicals or drugs specifically developed to destroy unknown cancer cells or impede their growth. Advances in cancer biology have led to the development of an ever-increasing number of chemotherapy agents. While each agent has a unique mechanism of action, each is also governed by basic principles.

As previously mentioned, the hallmark of cancerous tumors is unregulated cell growth. Cell division, be it among healthy or cancerous cells, occurs via the cell cycle. The cell cycle is an ordered set of events that has multiple phases, involving a resting phase, active phase, growing phase, and mitosis or cell division. The role of chemotherapy is to interfere with a particular phase of the cell cycle and cause its death.

There are four main types of chemotherapy agents used in the treatment of adjuvant breast cancer. They are, alkylating agents, antimetabolite agents (anthracycline-based), antitumor antibiotics, and plant alkaloids, also commonly referred to as taxanes. Organized with respect to the major classifications, Table 2 shows the most commonly used chemotherapy agents (according to their drug name or common trade name) and their mechanism of action (Cancer Care Ontario Formulary, 2004/2005, 2005, 2006). This table also provides information on the blood-brain-barrier (BBB) permeability of these agents.

Randomized clinical trials have been employed to evaluate the efficacy of adjuvant chemotherapy. While single-agent chemotherapy was found to diminish the likelihood of recurrence, given the heterogeneity of most cancer cells, polychemotherapy or the combination of several single-agent drugs into a regimen confers a superior benefit (Early Breast Cancer Trialists' Collaborative Group, 2005). Randomized clinical trial data comparing a regimen of adjuvant chemotherapy to no-adjuvant chemotherapy was shown

Table 2. Common single-agent chemotherapies with a general description of the modes of action, and whether or not the agent is known to cross the blood-brain-barrier.

Chemotherapy agent	Mode of action*	Permeation of BBB?*
<u>Alkylating agents</u>	Directly attacks DNA	
Cyclophosphamide (C)	Damages cross-linking DNA	Yes, including metabolites
<u>Antimetabolite agents</u>	Interferes with DNA synthesis	
<u>(anthracycline-based)</u>		
Flourouracil (F)	Pyrimidine antagonist	Yes
Methotrexate (M)	Folic acid antagonist	Poorly
<u>Antitumor antibiotics</u>	DNA-damaging agents	
Doxorubicin (A)	Damages DNA via different methods or by generation of free radicals	No
Epirubicin (E)	Inhibits DNA and RNA synthesis; precise mechanism is unknown	No
<u>Plant alkaloids</u>	Interference with actions of microtubules	
<u>(taxanes)</u>		
Docetaxal (Taxotere)	Inhibition of microtubules used in cell division and replication	No information found
Paclitaxel (Taxol)	Inhibition of microtubules used in cell division and replication	No

Notes. * = Cancer Care Ontario Formulary (2004/2005; October, 2005; February, 2006);

BBB = blood-brain-barrier.

to robustly reduce the risk of recurrence and improve overall survival in early stage breast cancer (Early Breast Cancer Trialists' Collaborative Group, 1998, 2005).

Some of the most widely used polychemotherapy regimens (past and present) for the treatment of early stage breast cancer are presented in Table 3 (Early Breast Cancer Trialists' Collaborative Group, 2005; Gradishar, 2003). This table also describes the

standard dosage and typical number of chemotherapy cycles administered per regimen. Compared to even several years ago, there is a substantially lower threshold for recommending adjuvant chemotherapy for early stage breast cancer (Harlan et al., 2006; Piccart et al., 2005), and concomitantly, greater use of aggressive dosing schedules (e.g., a complete cycle in two weeks instead of the typical three-week schedule; Gradishar, 2003). Research on patient preferences has found that when given the choice, breast cancer patients will opt for the more toxic treatment even if the benefits are minimal (e.g., 1% improvement in survival; Slevin et al., 1990).

Although no longer in widespread use in the adjuvant category, CMF was the benchmark of care for many years (Hudis, 2005) and is reported herein (see Table 3) because many of the studies examining chemotherapy-induced cognitive decline (to be fully reviewed in an upcoming section) were based on this regimen. The CMF regimen was replaced by newer anthracycline-based treatment protocols that were found to show a superior benefit (Early Breast Cancer Trialists' Collaborative Group, 1998, 2005). Among the anthracyclines, there does not appear to be any significant heterogeneity between them; for instance, the two most common anthracycline-based regimens are FEC and FAC, both of which show a similar efficacy and benefit profile (Early Breast Cancer Trialists' Collaborative Group, 2005). More recently, the introduction of taxanes to the adjuvant setting has shown considerable promise. An anthracycline-taxane combination has been reported to be superior in terms of efficacy compared to solely anthracycline-based regimen (Dang, 2006; Piccart et al., 2005; Trudeau, Eisen, Messersmith, Sinclair, Pritchard, & Members of the Breast Cancer Disease Site Group, 2006).

Table 3. Common adjuvant chemotherapy regimens used in the treatment of early stage breast cancer.

Regimen	Chemotherapy agents	Standard chemotherapy regimen
<u>Past regimen</u>		
CMF	Cyclophosphamide, methotrexate, fluorouracil	6 cycles of C (100 mg/m ² orally days 1-14), M (40 mg/m ² IV days 1 & 8), F (600 mg/m ² IV days 1 & 8), repeat every 28 days
<u>Current regimens</u>		
<u>Standard anthracycline-based regimens</u>		
AC	Doxorubicin (A), cyclophosphamide (C)	4 cycles of A (60 mg/m ² IV day 1), C (600 mg/m ² IV day 1), repeated every 21 days
CAF/(FAC)	Cyclophosphamide (C), doxorubicin (A), fluorouracil (F)	6 cycles of C (100 mg/m ² orally days 1-14), A (30 mg/m ² IV days 1 & 8), F (500 mg/m ² IV days 1 & 8), repeat every 28 days
FEC-100	Fluorouracil (F), epirubicin (E), cyclophosphamide (C)	6 cycles of F (500 mg/m ² IV day 1), E (100 mg/m ² IV day 1), C (500 mg/m ² IV day 1), repeat every 21 days
CEF	Cyclophosphamide (C), epirubicin (E), fluorouracil (F)	6 cycles of C (75 mg/m ² orally days 1-14), E (60 mg/m ² IV days 1 & 8), F (500 mg/m ² IV days 1 & 8), repeat every 28 days
<u>Taxane-containing regimens</u>		
AC-Taxotere	Doxorubicin (A), cyclophosphamide (C), - Taxotere (Docetaxel)	AC x 4 cycles: (60 mg/m ² IV day 1) C (600 mg/m ² IV day 1), repeat every 21 days, THEN 4 cycles Docetaxel (100 mg/m ² IV day 1), repeat every 21 days
AC-Taxol	Doxorubicin (A), cyclophosphamide (C), - Taxol (Paclitaxel)	AC x 4 cycles: A (60 mg/m ² IV day 1) C (600 mg/m ² IV day 1), repeat every 21 days, THEN 4 cycles Paclitaxel (175 mg/m ² IV day 1 (3 hr infusion), repeat every 21 days

Note: IV = intravenous

Regrettably, in their effort to eliminate cancerous cells, many adjuvant chemotherapy agents also destroy healthy cells. Medical complications secondary to adjuvant chemotherapy (although rare in some circumstances) may include nausea and/or vomiting, diarrhea or constipation, hair loss, loss of appetite, mouth sores, anemia, fatigue, infertility, lowered immune response and increased vulnerability to infection, decreased platelet count, renal difficulties, and damage to the heart muscle (American Cancer Society, 2006). Antiemetics and antibiotics have helped to improve the acute tolerability of chemotherapy treatment (Grunberg & Hesketh, 1993) and over time the healthy cells may regenerate. Additionally, patients may also experience longer lasting health effects in the form of a chemotherapy-induced or accelerated menopause (Fournier, Modi, Panageas, Norton, & Hudis, 2005).

Adjuvant hormonal therapy. Hormonal treatment is usually recommended to women who have ER+ tumors (Breast Cancer Disease Site Group, 2002). Over the last 20 years, the gold standard in adjuvant hormonal treatment for early stage breast cancer patients has been a selective estrogen receptor modulator called tamoxifen (Jones & Buzdar, 2004). Tamoxifen is approved as an anti-estrogen therapy for both pre- and post-menopausal breast cancer patients with ER+ tumor receptors (Breast Cancer Disease Site Group, 2002). In breast tissue, tamoxifen exerts antagonist properties, binding itself to the nucleus of breast cancer cells and serving to slow or halt the unregulated growth of cancerous tissue (Angelopoulos, Barbounis, Livadas, Kaltasas, & Tolis, 2004; Kudachadkar & O'Regan, 2006). However, in other tissues such as the endometrium and bone, tamoxifen exerts partial agonist properties, the consequences of which depend on the tissue affected and may be detrimental or beneficial (discussed further below).

The current standards of practice recommend that tamoxifen be prescribed in a single pill form, at a dosage of 20 milligrams per day, for five years of uninterrupted therapy (National Institute of Health, 2000; Eisen, Trudeau, Shelley, Sinclair, & the Breast Cancer Disease Site Group, 2005). Depending on the specific disease and patient characteristics, adjuvant tamoxifen may be prescribed alone (monotherapy), simultaneously with chemotherapy (concurrent chemoendocrine therapy), or following chemotherapy (sequential chemoendocrine therapy; Early Breast Cancer Trialists' Collaborative Group, 2005). When both hormonal and chemotherapy treatments are recommended, sequential chemoendocrine therapy provides a superior benefit (Albain et al., 2004 as cited in Early Breast Cancer Trialists' Collaborative Group, 2005).

When employed in the long-term, adjuvant tamoxifen has been associated with certain adverse effects. The partial agonist activity of the compound contributes to an increased likelihood of developing endometrial cancer, thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism), and stroke (Astrazeneca, 2005; Cochrane Breast Cancer Group, 2005; Fisher et al., 1994; McDonald, Alexander, Whyte, Forrest, & Stewart, 1995; Swerdlow & Jones, 2005; van Leeuwen et al., 1994). Despite these risks, there remains an overall net treatment benefit of taking tamoxifen that reduces the chance of recurrence (Early Breast Cancer Trialists' Collaborative Group, 2005). The most well-known health advantage associated with prolonged tamoxifen use, also a consequence of the compound's partial agonist properties, is a beneficial effect on bone mass and bone density (Benshushan & Brzezinski, 1999); Fisher et al. (1998) reported a 19% reduction in osteoporotic hip fractures among long-term tamoxifen users.

The majority of self-reported complaints related to tamoxifen use were vasomotor (e.g., hot flashes, night sweats) and gynaecological in nature (e.g., hypomenorrhea,

amenorrhea, vaginal dryness, vaginal bleeding, pain during intercourse, vaginal discharge; Nolvadex Adjuvant Trial Organisation, 1985; Ribeiro & Swindell, 1988), the most bothersome of which tended to be hot flashes occurring during the first year of treatment (Benshushan & Brzezinski, 1999; Love, Cameron, Connell, & Leventhal, 1991). The behavioural manifestation of vasomotor symptoms was considered to be the consequence of anti-estrogenic effects acting on the hypothalamus (Paganini-Hill & Clark, 2000) and as such was postulated to cross the BBB (Kreukels, Schagen, Ridderinkhof, Boogerd, Hamburger, & van Dam, 2005). The effects of tamoxifen and other similar agents on neuropsychological function is discussed more broadly in the context of hormonal effects and cognition in the upcoming section entitled, "Specific factors that may influence neuropsychological function." Finally, it is noteworthy that tamoxifen is not related to an increased incidence of depression (Day et al., 1999).

Today, tamoxifen has been deployed to more than one million women worldwide in an effort to lower the risk of recurrence and improve survival rates (Benshushan & Brzezinski, 1999; Early Breast Cancer Trialists' Collaborative Group, 2005). Among women with ER+ disease, the combination of chemotherapy and tamoxifen confers a superior benefit to that of tamoxifen alone (Early Breast Cancer Trialists' Collaborative Group, 2005). For middle-aged women with ER+ status, the mortality rate due to breast cancer is approximately halved when treatment includes a six-month schedule of an anthracycline-based chemotherapy (e.g., FAC or FEC) followed by five years of tamoxifen.

Over the last five years, increasing attention has been paid to a different generation of estrogen blockers known as aromatase inhibitors (e.g., arimidex, aromasin, femara). Unlike tamoxifen that block's cancerous cells from using estrogen, aromatase inhibitors reduce the overall amount of circulating estrogen in bodily tissues via aromatase (Goss &

Strasser, 2001). Aromatase inhibitors are unable to influence estrogen that is produced by the ovaries and is therefore recommended to patients who have reached menopause (Cancer Care Ontario Formulary, 2006; National Cancer Institute, 2006). The most common of the aromatase inhibitors is arimidex, and it is administered in a similar manner to tamoxifen, in a daily, self-administered, oral dose (1 mg) for five years (Eisen et al., 2005).

In a landmark randomized clinical trial of more than 9000 postmenopausal, early stage breast cancer patients with ER+ tumors, efficacy comparisons were made between arimidex plus tamoxifen placebo, tamoxifen plus arimidex placebo, or a combination of arimidex and tamoxifen (The ATAC [Arimidex, Tamoxifen Alone or in Combination] Trialists' Group, 2003). The likelihood of relapse was significantly reduced in the arimidex arm, although overall survival remained the same in both groups. In terms of toxicity, arimidex has been associated with a greater incidence of myocardial infarction and loss of bone mineral density (Eisen et al., 2005). Given these latter concerns in combination with the lack of a survival benefit, the recommended standard of care among postmenopausal women with ER+ tumors in the province of Ontario (at the time of this writing) is adjuvant tamoxifen (Eisen et al., 2005). Adjuvant arimidex is recommended in cases where tamoxifen is contraindicated or following two to three years of tamoxifen therapy, as based on relatively new, emerging evidence (Eisen et al., 2005).

Neuropsychological effects of chemotherapy

Several investigative teams have attempted to identify the incidence, severity, and underlying mechanisms of chemotherapy-induced neuropsychological decline in breast cancer patients. Formal investigations of this phenomenon have mainly consisted of retrospective, cross-sectional designs with comparison groups comprising the

standardization sample (published norms), healthy age-matched controls or persons with a similar breast cancer diagnosis but who did not receive adjuvant chemotherapy. While follow-up data are emerging for a small number of these studies, a lack of pre-treatment, baseline assessment of neuropsychological function hampers efforts to conclude that observed deficits are the result of adjuvant chemotherapy.

A call for a more rigorous research methodology, particularly in the form of prospective designs, has been emphasized throughout the literature (e.g., Ahles & Saykin, 2001; Anderson-Hanley et al., 2003; Castellon et al., 2004; Cimprich, So, Ronis, & Trask, 2005; Donovan et al., 2005; Rugo & Ahles, 2003; Schagen, Muller, Boogerd, & van Dam, 2002; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004; Wefel, Lenzi, Theriault, Buzdar, Cruickshank, & Meyers, 2004). While there has been a delay in such published reports, it may be the consequence of the labor- and cost-intensive nature of a longitudinal design involving a clinical sample. Apart from our own study (Stewart, Collins, Mackenzie, Tomiak, Verma, & Bielajew, submitted for publication), there are five published articles detailing the results of a pre-treatment neuropsychological assessment with short- and/or long-term re-test data. To better understand the relationship between adjuvant chemotherapy and neuropsychological decline in early stage breast cancer, this section of the thesis is devoted to a critical summary of relevant studies that comprise original data. Prospective studies are presented first, followed by a review of the many cross-sectional studies and any associated follow-up data. The supporting evidence (e.g., electrophysiological studies) for the observed deficits is also described. Taken together, these results are summarized in the context of numerous qualitative reviews and a single quantitative, meta-analysis conducted by Falletti et al. (2005). Note that an overview of the

major factors that can influence performance on neuropsychological measures pertinent to this population is provided in the next segment.

Prospective studies

A list of the prospective studies investigating chemo fog in breast cancer can be found in Table 4. Two of the studies are from the same research group, that being Shilling et al. (2005) and Jenkins et al. (2006). To better understand the influence of chemo fog on older breast cancer patients, Hurria et al. (2006) conducted a pilot prospective study; these results are also reviewed. Wefel, Lenzi, Theriault, Davis et al. (2004) conducted the first prospective study in this research area and their results are summarized first.

Wefel, Lenzi, Theriault, Davis et al. (2004) investigated neuropsychological decline in a sample of 18 newly diagnosed breast cancer patients. All participants underwent comprehensive neuropsychological testing prior to the commencement of adjuvant treatment (baseline interval). Following six courses of FAC, the neuropsychological tests were re-administered, a minimum of three weeks following completion of any antiemetic or other medication that could have compromised cognitive function (short-term interval). Next, a subgroup of participants ($n = 6$) was randomized (as part of a clinical trial) to receive four courses of methotrexate/vinblastine, this prior to the final phase of neuropsychological evaluation conducted at 18 months post-baseline (long-term interval). All participants also completed questionnaires related to affective function (Minnesota Multiphasic Personality Inventory, Scales 2 [Depression] and 7 [Psychasthenia/Anxiety]; Klove, 1963) and quality of life (Functional Assessment of Cancer Therapy-Breast Module [Cella, 1996]). At the time of study enrolment, half of the participants were pre-

Table 4. List of prospective studies evaluating chemotherapy-induced cognitive decline (in alphabetical order).

Bender, C.M., Sereika, S.M., Berga, S.L., Vogel, V.G., Brufsky, A.M., et al. (2006). Cognitive impairment associated with adjuvant therapy in breast cancer. <i>Psycho-Oncology</i>, 15, 422-430. Hurria, A., Rosen, C., Hudis, Zuckerman, E., Panageas, K.S., et al. (2006). Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: A pilot prospective longitudinal study. <i>Journal of American Geriatric Society</i>, 54, 925-931. Jenkins, V., Shilling, V., Deutsch, G., Bloomfield, D., Morris, R., et al. (2006). A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. <i>British Journal of Cancer</i>, 94, 828-834. Shilling, V., Jenkins, V., Morris, R., Deutsch, G., & Bloomfield, D. (2005). The effects of adjuvant chemotherapy on cognition in women with breast cancer- preliminary results of an observational longitudinal study. <i>The Breast</i>, 14, 142-150. Wefel, J.S., Lenzi, R., Theriault, R.L., Davis, R.N., & Meyers, C.A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma. <i>Cancer</i>, 100, 2292-2299.
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menopausal. The mean age and highest level of education of the sample was 45.4 years (standard deviation [SD] = 6.7) and 14.0 years (SD = 2.6), respectively.

Given that original data from a control group were not collected, Wefel, Lenzi, Theriault, Davis et al. (2004) compared their results to a historical control group, that is, published norms. Cognitive impairment was defined below 2 SD on at least one measure or below 1.5 SD on at least two measures; this corresponds to the 6.5th and 2nd percentiles in the normal population, respectively. Using this criterion, 33% (n = 6) of the sample was considered cognitively impaired at baseline, with verbal learning and memory the cognitive

domains most affected. Differences between those defined as impaired versus not impaired were unrelated to demographic or disease characteristics (e.g., tumor stage).

Additionally, change in cognitive functioning between test intervals was assessed using the reliable change index (RCI). Using the standard error of measurement of each test, the RCI is defined as the 90% confidence interval for the difference in test results in the event that no real change has occurred. At the short-term interval, 61% ($n = 11$) of the sample was found to be cognitively impaired as measured using the RCI. Decline was noted on tasks of attention and working memory (Arithmetic subtest of the Wechsler Adult Intelligence Scale – Revised [WAIS-R; Wechsler, 1981], Digit Span subtest of the WAIS-R), verbal learning (Verbal Selective Reminding Test Long-term Storage [Reitan & Davison, 1974]), and executive function (Trail-Making Test [Reitan & Davison, 1974]). Those who exhibited cognitive decline at the short-term assessment could not be distinguished from those who did not on the basis of pre-treatment cognitive functioning, age, education, menopausal status, mood, radiotherapy, or tumor stage. While there were no differences in quality of life between the two groups, there was some indication that self-reported ability to work was lower among those who declined.

At the long-term interval, there were no group differences between those who received FAC alone or FAC combined with methotrexate/vinblastine. As such, both groups were combined for all analyses. There were no significant group differences between the short- and long-term interval on any of the cognitive tests. Among those who exhibited cognitive decline at the short-term interval, 45% exhibited improvement, 45% demonstrated stable cognitive function, while the remaining 10% of participants showed a mixed pattern of stabilization and improvement at long-term follow-up. Also of interest is

that self-reported ability to work had also improved. Depression and anxiety scores were not correlated with any of the objective cognitive measures (all p 's $\geq .02$).

This study (Wefel, Lenzi, Theriault, Davis et al., 2004) marks one of the few to methodologically consider the impact of co-medications (e.g., antiemetics) on cognitive performance. Nonetheless, this work has been criticized because the investigators did not correct for multiplicity, possibly inflating the extent of neuropsychological impairment (Fan et al., 2005). While this may be the case, the authors did set their alpha level at .01 for the paired sample t -tests (baseline versus short-term tests) and also used binomial tests to compare observed frequencies with those expected under normal circumstances. Finally, notwithstanding the small sample size, these findings suggest that there was no further deterioration between short- and long-term retests, with almost half of participants showing partial recovery in neuropsychological function, approximately 12-months after completion of adjuvant chemotherapy.

As part of an ongoing, longitudinal study investigating the cognitive effects of adjuvant chemotherapy among early stage breast cancer patients, Shilling et al. (2005) published preliminary results from the first half of their sample to have completed both pre-adjuvant treatment assessment and short-term cognitive evaluation. The experimental and comparison groups consisted of 50 breast cancer patients and 43 healthy controls, respectively. All breast cancer participants received a chemotherapy regimen of six cycles of FEC. The neuropsychological battery that was administered sampled the main cognitive domains and was conducted at baseline and four weeks following the last chemotherapy cycle (six months in the control group). All participants also answered questions about cognitive failures in everyday life, psychological morbidity, and quality of life. There were no significant differences in age, education, or IQ between the two groups.

At baseline, significant group differences were found on only 2 of 14 measures with the healthy controls outscoring breast cancer patients in both instances (Letter cancellation task, $p = .02$ and Logical Memory II subtest of the Wechsler Memory Scale – Third edition [WMS-III; Wechsler, 1997a], $p = .03$). At short-term follow-up, healthy control participants demonstrated a practice effect on all tests, while performance among the breast cancer group gave rise to three significant group by time interactions in which the experimental participants failed to benefit from repeated exposure to the material (Rey Auditory-Learning Test, Trials 1-5 [Rey, 1964], $p = .005$; Letter-Number-Sequencing subtest of the WMS-III, $p = .037$; Rey Auditory-Verbal Learning Test, first presentation, $p = .031$).

Shilling et al. (2005) also evaluated individual differences in performance using the RCI method with a modification to also take into account practice effects. Reliable cognitive decline was defined as decline on two or more tests. Using this criterion, 34% ($n = 17$) of breast cancer patients compared to 18.6% ($n = 8$) of healthy controls showed cognitive decline. Overall, the experimental group was 2.25 times more likely than their healthy counterparts to be classified as cognitively impaired ($\chi^2 = 2.8$, $p = .0475$). Among those who exhibited cognitive decline, there were not a significantly greater number of self-reported cognitive failures encountered in everyday life. Cognitive failures were related to quality of life and psychological morbidity and thus appear to be more likely the consequence of emotional functioning instead of cognitive decline (Shilling et al., 2005).

As a follow-up to Shilling et al. (2005), Jenkins et al. (2006) published a three-year prospective study evaluating the short- and long-term effects of adjuvant chemotherapy. The final cohort consisted of 85 women with early stage breast cancer scheduled to receive

chemotherapy, 43 women scheduled to receive endocrine therapy and/or radiotherapy, and 49 healthy control subjects. Participants were tested at baseline, shortly after chemotherapy (6-month interval) and at 18-months after baseline testing. The investigators used the same modified RCI method to compute individual change and definition of reliable cognitive decline (decline on 2 or more cognitive measures) as Shilling et al. (2005).

After taking age and intelligence into account, there were no significant main effects of group or significant interactions. At the short-term interval, compared to baseline performance, 20% of chemotherapy patients, 26% in non-chemotherapy patients, and 18% of healthy controls met the criterion for reliable cognitive decline. At the long-term interval, these findings were 18%, 14%, and 11%, respectively. These results were unrelated to psychological distress, quality of life indices, and self-reported cognitive failures. Reliable cognitive decline occurred more frequently in the two patient groups compared to the healthy control subjects, but there was not a statistically significant difference between them at either time point. The investigators concluded that while a few breast cancer patients sustained reliable cognitive loss, the majority of them were either unaffected by their treatment or improved over time. It was queried whether a more robust effect of adjuvant chemotherapy was not observed because the majority of participants received a low dose of FEC.

Bender et al. (2006) investigated cognitive decline associated with adjuvant therapy in three groups of patients. Group 1 comprised 19 stage I or II, ER- breast cancer patients scheduled to receive adjuvant chemotherapy only. Group 2 consisted of 15 stage I or II, ER+ breast cancer patients slated to receive adjuvant chemotherapy plus tamoxifen. The control group (Group 3) was made up of 12 patients diagnosed with ductal carcinoma in situ who, besides surgery, were not expected to receive either adjuvant chemotherapy or

tamoxifen. All participants were tested at three time intervals: (i) prior to chemotherapy treatment in Groups 1 and 2 and after surgery in Group 3 (Time 1), (ii) within one week of completing chemotherapy treatment in Groups 1 and 2, and at an equivalent time point in Group 3 (Time 2), and (iii) one-year after the second assessment in all three groups (Time 3). All participants were pre- or peri-menopausal. The overall sample was young, 42.6 years old (standard error of the estimate [SEM] = 5.4) and had 14.3 years of education (SEM = 2.7). Neuropsychological function was measured using a battery of tests spanning all major domains of cognitive function. The Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996) was used to estimate depressive symptomatology and the Profile of Mood States (POMS; McNair, Lorr, & Droppelman, 1992) to assess anxiety and fatigue. Self-reported cognitive function and data regarding medication use were also gathered. The cognitive battery and questionnaires took about 90 minutes to complete. Most breast cancer patients in Groups 1 and 2 received a cyclophosphamide-containing regimen, either CMF or cyclophosphamide and doxorubicin. Use of concomitant medication was equal among the three groups.

At Time 2, there were no significant group differences. Overall cognitive performance of the control group significantly improved from Time 2 to Time 3; assumed to be due to practice effects. Among the patient groups however, overall performance on cognitive measures fell between Time 2 and Time 3 evaluations; cognitive loss was even greater than that due to practice effects alone. Participants who received chemotherapy only showed declines in verbal working memory tasks. Among those treated with chemotherapy plus tamoxifen, performance on visual memory and verbal memory tasks was below expected levels. Self-reported cognitive complaints, depressive symptoms, anxiety, and fatigue indices were more likely related to each other rather than cognitive test

scores. While these investigators reported many marginally significant findings ($p < .10$ or less), given that they did not account for Type I error rates, the results significantly overestimate the frequency of cognitive decline. Nevertheless, these results show a clear trend that adjuvant chemotherapy negatively influences cognitive function with some evidence that the addition of tamoxifen increases the likelihood of cognitive deterioration among early stage breast cancer patients exposed to these treatments.

Hurria et al. (2006) conducted a pilot, prospective study of the chemo fog phenomenon in a sample of 28 newly diagnosed, *older* breast cancer patients. The mean age of the sample was 71 years old. Most patients received a chemotherapy regimen of CMF, AC, or AC with paclitaxel. Eighty-nine percent of the participants also received adjuvant hormonal treatment following completion of chemotherapy. All major domains of neuropsychological function were assessed using standardized measures. A total of 12 test scores were generated from this battery. Other information relevant to the geriatric population was gathered, including measures to assess functional status (activities of daily living), instrumental activities of daily living, depression, and quality of life indices. All participants were tested prior to the start of adjuvant chemotherapy and six months following completion of chemotherapy.

Raw test scores were converted into standardized scores using normative data. Cognitive decline was defined as scoring two SD below published norms on two or more measures. At baseline, three participants (11%) met this criterion. Six months following completion of chemotherapy, eight participants (29%) met this cutoff. Looking at the change in performance for each individual, while still using the same criterion, 14 participants (50%) showed no change in cognitive function, 11 participants (39%) showed a decline, and 3 (11%) showed an improvement ($p = .05$). Areas of cognitive decline most

affected were in visual memory, spatial function, psychomotor speed, and attention. Among those who showed a decline, 91% received CMF. Cognitive decline was not associated with any geriatric assessment measures including functional status and activities of daily living. Although these investigators identified a subset of patients who sustained treatment-related cognitive loss, the lack of a control group precluded the extent of cognitive decline that may be attributed to normal age-associated cognitive decline.

In summary, with the exception of the findings from Jenkins et al. (2006), the data from these prospective investigations provide support for adjuvant chemotherapy-induced cognitive decline in a minority of breast cancer patients. This cognitive decline has been identified as subtle in nature.

Retrospective studies

A list of the main retrospective studies contributing original data and any associated follow-ups appears in Table 5. Of these 11 papers, all but two provided sufficient evidence to support the notion of chemotherapy-induced neuropsychological decline in early stage breast cancer. Given that this represents the bulk of the evidence to date, each of these studies is summarized in considerable detail below. This allows for a better appreciation of the methodological nuances that may have influenced the subtle nature of this phenomenon.

Wieneke & Dienst (1995) and Wieneke (1992) are widely regarded as the first investigators to systematically evaluate the cognitive side effects associated with adjuvant chemotherapy treatment for early stage breast cancer. These investigators recruited a sample of 25 Stage I or II breast cancer patients who had completed adjuvant chemotherapy treatment an average of 6.6 months earlier (SD = 4 months; range: 0.5 - 12 months). Additionally, three participants were on a customary resting period (as per protocol) and

Table 5. List of retrospective studies and any associated follow-up studies evaluating chemotherapy-induced cognitive decline (in alphabetical order).

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- Ahles, T.A., Saykin, A.J., Furstenberg, T., Cole, B., Mott, L.A., Skalla, K., al. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *Journal of Clinical Oncology*, 20, 485-493.
- Brezden, C., Phillips, K-A., Bunston, T., & Tannock, I.F. (2000). Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *Journal of Clinical Oncology*, 18, 2695-2701.
- Castellon, S.A., Ganz, P.A., Bower, J.E., Petersen, L., Abraham, L., & Greendale, G.A. (2004). Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *Journal of Clinical and Experimental Neuropsychology*, 26, 955-969.
- Donovan, K.A., Jacobsen, P.B., Andrykowski, M.A., Winters, E.M., Balducci, L., Malik, U. et al. (2004). Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. *Journal of Pain and Symptom Management*, 28, 373-380.
- Fan, H.G., Houede-Tchen, Yi, Chemerynsky, I., Downie, F.P., Sabate, K., & Tannock, I.F. (2005). Fatigue, menopausal symptoms, and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study. *Journal of Clinical Oncology*, 23, 8025-8032.
- Schagen, S.B., van Dam, F.S.A.M., Muller, M.J., Boogerd, W., Lindeboom, J., & Bruning, P.F. (1999). Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *American Cancer Society*, 85, 640-650.
- Schagen, S.B., Muller, M.J., Boogerd, W., Rosenbrand, R.M., van Rhijn, D., Rodenhuis, S., & van Dam, F.S.A.M. (2002). Late effects of adjuvant chemotherapy on cognitive function: A follow-up study in breast cancer patients. *Annals of Oncology*, 13, 1387-1397.
- Scherwath, A., Mehnart, A., Schleimer, B., Schirmer, L., Fehlauer, F., Kreienberg, R., et al. (2006). Neuropsychological function in high-risk breast cancer survivors after stem-cell supported high-dose therapy versus standard-dose chemotherapy: Evaluation of long-term treatment effects. *Annals of Oncology*, 17, 415-423.
- Tchen, N., Juffs, H.G., Downie, F.P., Yi, Q.-L., Hu, H., Chemerynsky, I. et al. (2003). Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology*, 21, 4175-4183.
- van Dam, F.S.A.M., Schagen, S.B., Muller, M.J., Boogerd, W., Wall, E.V.D., Fortuyn, M.E.E., & Rodenhuis, S. (1998). Impairment of cognitive function in women receiving
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adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose chemotherapy. *Journal of the National Cancer Institute*, 90, 210-218.

Wieneke, M.H., & Dienst, E.R. (1995). Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. *Psycho-oncology*, 4, 61-66.

had completed only half of their six-month course of adjuvant chemotherapy. Overall, the duration of chemotherapy treatment ranged from 3 to 18 months, the average course lasted 6.7 months (SD = 3 months). Seventeen participants received a standard protocol of CMF only, four received CAF alone, and seven were treated with CMF followed by CAF. At the time of evaluation, 39% of the study cohort were taking tamoxifen. Patients were highly educated, with 93% having had some university education, 29% of which had had graduate training. The estimated full scale IQ of the sample was 112.9 (SD = 5.3; min - max: 96 - 120), corresponding to the 81st percentile (High Average range) in the general population. The mean age in years of the sample was 42 (SD = 6.7 years). Cognitive functioning of patients was assessed using standardized measures falling into nine major cognitive domains with a total of 16 neuropsychological test scores reported. Depression was evaluated via clinical interview and the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

Compared to published norms, group performance was within the normal range or higher on the domains of attention/concentration, abstract/conceptualization, and language function. A multivariate analysis revealed significantly lower performance on memory ($p < .0001$), mental flexibility/speed of processing ($p < .009$), and visuospatial function ($p < .001$). Apparent cognitive loss was not related to time since treatment, depression, or type of chemotherapy, but was significantly related to duration of treatment (Spearman's $\rho =$

.39, $p < .01$). At the level of the individual patient, 75% of the sample was moderately impaired, based on a score of at least two standard deviations below the normative mean on at least one neuropsychological measure. The investigators concluded that the pattern of impairment was not consistent with global deficits and was mostly compatible with subcortical localization as a consequence of slowed processing speed as well as memory disturbance.

The extent of cognitive impairment in this group of breast cancer patients marks the highest prevalence rate of all the major studies in this research area. This may be a function of the somewhat lenient criteria used to define cognitive impairment herein. Nevertheless, these scores were surprising given that premorbid IQ places the cohort nearly one SD above the mean while 75% of the sample placed at least two SDs below the mean on at least one measure. Additionally, the investigators concluded that the neuropsychological deficits were mostly consistent with subcortical rather than diffuse, cortical brain damage; this was based on the tenet that verbal fluency skills were intact. Verbal fluency skills are highly influenced by education (Spreen & Strauss, 1998) and given that this cohort was greatly skewed towards this advantage, this may have impacted test findings.

A group of researchers from The Netherlands Cancer Institute have made important contributions to this field of research through the publication of two cross-sectional design studies in the 1990's and a follow-up report shortly thereafter (Schagen et al., 1999; Schagen, Muller, Boogerd, Rosenbrand et al., 2002; van Dam et al., 1998). Furthermore, to better elucidate the underlying mechanisms of chemotherapy-induced cognitive dysfunction, this group (Kreukels et al., 2005; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001) incorporated electroencephalography (EEG) and event related potentials

(ERP) as a method to monitor brain activity during data collection. These findings are briefly summarized.

In the first of these cross-sectional designs (van Dam et al., 1998), breast cancer participants with stage II or III grade tumors were *randomly* assigned (post-surgery) to receive either high dose chemotherapy (four cycles of FEC followed by a fifth cycle of high dose cyclophosphamide, thiotepa, and cyclophosphamide [CTC]; $n = 34$) or a standard dose arm (four or five cycles of FEC only; $n = 36$). Any confound related to disease severity was thus minimized through randomization, a practice apropos, although no longer permitted (Fan et al., 2005). Treatment also included local surgery, local radiation therapy, and tamoxifen for two years. A third group of 34 participants with stage I disease received local surgery and radiation therapy, but no systemic treatment and no hormonal treatment, thus serving as the comparison group.

Participants underwent a two-hour cognitive assessment of the major areas of functioning roughly two years post-chemotherapy; patients in the control group had completed treatment about 2.5 years earlier. All participants also filled out a checklist of cognitive problems in everyday life, a standardized health-related quality of life survey, and the Hopkins Symptom Checklist (Ibbotson, Maguire, Selby, Priestman, & Wallace, 1994) to assess for psychological distress. Mean age and premorbid IQ did not differ as a function of group membership, although education was significantly lower in the control group. Due to the effects of adjuvant chemotherapy, the majority of patients in the two experimental groups were postmenopausal whereas this was only the case in less than half of the control counterparts. At the time of evaluation, alcohol consumption and use of psychoactive drugs and antiemetics was considered negligible among all participants.

Cognitive test performance of the control group appeared to be intact and was not significantly different from published norms. Moreover, there were no differences in cognitive performance among control participants who were pre- versus post-menopausal. Compared to the control group, participants randomized to the high dose arm scored significantly worse on 7 of 19 cognitive tests in the areas of attention/concentration, mental flexibility/working memory, speed of processing, visual memory, and motor function. However, all of these differences disappeared once the Bonferroni correction ($p < .002$) was applied to adjust for multiple comparisons.

Given that group means can mask cognitive decline at the individual level, neuropsychological functioning was also evaluated based on a cognitive impairment classification. Participants who scored a minimum of two standard deviations below the mean of the control group on at least three measures were considered cognitively impaired. According to this criterion, 32% of high dose patients, 17% of standard dose participants, and 9% of the controls sustained cognitive impairment. High dose participants experienced a risk of cognitive decline 8.5 times higher (95% confidence interval [CI] = 1.8 - 37.7, $p = .006$) compared to controls and 3.5 times higher relative to the standard dose arm (95% CI = 1.0-12.8, $p = .056$). While the latter finding did not achieve statistical significance, there was a trend to suggest that cognitive decline in this population is dose dependent (O'Shaughnessy, 2003a; van Dam et al., 1998). This is of particular salience because such differences could not be attributed to disease severity given the initial randomization of the two experimental groups. The likelihood of being classified as impaired was unrelated to previous/current use of tamoxifen (in the high dose arm), depression, anxiety, fatigue or time since treatment, even though the high dose arm reported significantly greater fatigue

and depression as compared to the control group. Medical charts were also reviewed for any illnesses' that could have accounted for the results; none were reported.

In a non-selected subgroup of this sample (18 high dose, 18 standard dose, and 14 controls), Schagen et al. (2001) investigated the possible underlying mechanisms of the cognitive dysfunction. Neurophysiological examination consisting of ERP (P300 component) latency and quantitative EEG analysis of the alpha peak frequency, alpha blocking, and asymmetry alpha rhythm. A single significant group difference was found on the asymmetry alpha rhythm although there was no indication of hemispheric asymmetry. By and large, the investigators reported little association between the neurophysiological parameters and neuropsychological performance. The only significant relationship found was between P300 latencies and test scores ($r = .30$, $p = .05$); longer latencies were associated with lower test scores. Indeed, Kreukels et al. (2005) found earlier and reduced P300 amplitude in breast cancer patients treated with CMF compared to non-chemotherapy treated breast cancer patients. Although tentative, the P300 component has been associated with attentional and working memory problems (Polich & Kok, 1995; Viaggiano, 1996 as cited in Schagen et al., 2001) and is certainly consistent with the observed, subtle deficits.

Employing the same cognitive test battery, criteria for defining cognitive impairment, and control group, as reported in the van Dam et al. (1998) study, Schagen and colleagues' (1999) recruited a sample of 20 breast cancer patients treated with six cycles of standard CMF plus tamoxifen and 19 persons treated with 6 cycles of CMF alone. The neuropsychological assessment took place almost 1.9 years post-chemotherapy. At the time of assessment, the experimental sample was 47.1 (SD = 6.5) years old. Twenty-eight percent of patients treated with chemotherapy were classified as impaired versus 12% in the control group (odds ratio = 6.4; 95% CI = 1.5 – 27.6; $p = .013$). Notable differences were

found in the areas of attention, mental flexibility and speed of processing, memory, word fluency, and slowed motor function in both hands. The elevated risk of cognitive impairment was not due to the inclusion of hormonal therapy in a subset of participants, fatigue, depression and anxiety status, or time since treatment. Self-reported cognitive complaints were not related to objective cognitive impairment, but were associated with emotional functioning.

To better understand the late effects of adjuvant chemotherapy on cognitive function, Schagen, Muller, Boogerd, Rosenbrand et al. (2002) conducted a follow-up of the two studies mentioned above. Using the same battery of neuropsychological tests, the participants were re-evaluated two years after the initial assessment or approximately four years following the last cycle of chemotherapy. Ineligibility due to breast cancer recurrence was in keeping with expected changes in disease status. There was, however, a high rate of attrition in the group identified as cognitively impaired following the first evaluation; 45% of the participants in the high dose CTC and 33% in the FEC standard dose dropped out. In the group who showed no impairments, there were no drop-outs. Ultimately, 22 of 34 CTC patients, 23 of 36 FEC patients, 31 of 39 CMF patients, and 27 of 34 controls completed follow-up testing.

The investigators reported that none of the previously observed differences between experimental and control groups with regard to cognitive impairment were observed at follow-up, suggesting that cognitive impairment attributed to adjuvant chemotherapy was transient. While findings from this study suggest that cognitive decline in a subset of breast cancer survivors is reversible, the large attrition rate seriously limited the generalizability of these results.

In a pilot study, a research group in Toronto (Brezden et al., 2000) investigated the short- and long-term effects of chemotherapy on cognitive function. A sample of 36 healthy, female volunteers served as the comparison group to two experimental groups consisting of breast cancer patients either undergoing standard dose chemotherapy (CEF or CMF) who had received at least two cycles ($n = 31$; short-term), or survivors who had completed chemotherapy a median of two years (minimum of 12-months) prior to cognitive testing ($n = 40$; long-term). The High Sensitivity Cognitive Screen (HSCS; Faust & Fogel, 1989) was employed as the cognitive measure. The test can be administered in only 30 minutes but is considered valid and reliable (Faust & Fogel, 1989) to predict formal neuropsychological function (normal, borderline, mild, moderate, or severe) in six cognitive domains: memory, language, visual-motor functioning, spatial function, attention-concentration, and self-regulation and planning.

After controlling for age, education, and menopausal status, moderate to severe impairment as categorized by the HSCS was found in 48% of patients (15 of 31) undergoing chemotherapy, 50% of patients (20 of 40) who had completed chemotherapy, and 11% of healthy controls (4 of 36). Not surprisingly, the overall frequency of cognitive impairment was significantly greater in both experimental groups compared to the control group. Differences in cognitive functioning were not attributable to mood states as measured by the Profile of Mood States.

Compared to other studies, Brezden et al. (2000) reported a higher prevalence of chemotherapy-induced cognitive impairment, but more significant than this, characterized the severity of cognitive decline to be similar to the clinical definition of neuropsychological impairment. This suggests that the level of cognitive decline is much more severe than originally thought. Not surprisingly, these findings have been scrutinized.

For instance, while 13% (4 of 31) of patients undergoing adjuvant chemotherapy and 20% (8 of 40) of patients who had already completed such treatment scored in the mildly impaired range, more than double or 44% (16 of 36) of the healthy controls also scored in the mildly impaired range. Castellon et al. (2004) aptly pointed out that this prompts one to be skeptical of either the screening measure (HSCS) or the control group. This research team has gone on to use this screening tool in combination with other commonly used neuropsychological measures to better understand cognitive decline secondary to adjuvant chemotherapy.

Using a much larger sample, this same group (Tchen et al., 2003) sought to disentangle the potentially confounding effects of fatigue and menopausal symptoms on chemotherapy-induced cognitive decline. They also wanted to determine the extent to which any of these factors influence overall quality of life. The experimental group consisted of 110 early stage breast cancer patients undergoing active treatment for their disease. At the time of diagnosis, the majority of participants were premenopausal ($n = 62$), having a median age of 48 years (range: 27 - 60) with some postsecondary education. The control group was composed of a patient-nominated, healthy sample (e.g., friend, relative, or neighbor) comparable in age, marital status, and educational background. Following exclusion due to ineligibility or participant refusal, the final sample consisted of 110 breast cancer patients and 107 controls, for a total of 100 matched pairs (accounting for ineligibility).

As in the pilot study (Brezden et al., 2000), a major component of the cognitive assessment included the HSCS. However, in addition, participants were also administered the Conner's Continuous Performance Test (Conners & Barta, 1967) to evaluate reaction time and sustained attention, and the Trail-Making Test, Parts A & B to assess for speed of

attention and concentration and visual-motor integration. Self-report data pertaining to fatigue, menopausal symptoms, and overall quality of life was captured using the Functional Assessment of Cancer Therapy (FACT), a well-known, empirically validated, series of questions. All participants filled out a 13-item questionnaire related to fatigue (FACT-F; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997), an 18-item survey on menopausal and sexual symptoms associated with endocrine function (FACT-ES; Fallowfield, Leaity, Howell, Beson, & Cella, 1999), and a 27-item questionnaire probing general quality of life involving physical, functional, family-social, and emotional domains (FACT-G; Cella et al., 1993).

At the time of the cognitive assessment, patients were receiving standard doses of common chemotherapy regimens; these were CEF, AC, CMF, and Other. Given that the neurotoxic effects of chemotherapy may be related to the number of administered cycles, the investigators measured cognitive performance a minimum of three cycles into their chemotherapy treatment. A very small minority of patients was receiving tamoxifen ($n = 5$) at the time of evaluation, while six patients were undergoing radiation therapy concurrently with chemotherapy.

The classification of cognitive function (normal, borderline, mild, moderate, or severe) was significantly worse in the patient groups ($p = .0008$), with 16% of breast cancer patients ($n = 16$) and 5% of controls ($n = 4$) exhibiting moderate or severe cognitive dysfunction. Even after age, education, and menopausal status were taken into account, statistically significant group differences were upheld ($p = .008$). Exploratory analyses revealed a trend for patients to perform more poorly compared to control participants on language, attention and concentration, and self-regulation and planning, with no differences found in memory related variables. Additionally, no group differences were reported for

either the Conner's Continuous Performance Test or the Trail-Making Test, although there were a small number of breast cancer participants who scored in the impaired range on the Trail-Making Test. This test measures speed for visual-motor scanning and attention (Army Individual Test Battery, 1944).

At the time of the assessment, only 25% of the experimental group was having menses (compared to 63% at diagnosis), suggesting that more than half of the experimental sample underwent an accelerated menopause. As expected, the breast cancer group experienced substantially worse menopausal symptoms than their control counterparts ($p < .0001$). The experimental group also sustained significantly more symptoms of fatigue (e.g., "difficulty starting and finishing tasks"; $p < .0001$).

Using a multivariate analysis with a preset significance level of .01, the classification of cognitive dysfunction among breast cancer patients was not significantly altered by fatigue, emotional well-being, number or type of chemotherapy treatment, menopausal symptoms, or hemoglobin levels at the time of assessment. In contrast, multivariate analyses revealed that fatigue was highly influenced by the severity of menopausal symptoms ($p < .0001$), emotional well-being ($p = .004$), and hemoglobin at the time of the assessment ($p = .006$), with a possible trend towards type of chemotherapy ($p = .06$). Influential variables on menopausal symptoms showed a tendency for persons with chemotherapy-induced menses to have worse menopausal symptoms ($p = .03$). In terms of quality of life, it was profoundly influenced by fatigue ($p < .0001$) and menopausal symptoms ($p < .0001$), but not at all by HSCS scores. In total, fatigue, menopausal symptoms, and quality of life were strongly associated with each other (in all cases significance level was $p < .0001$, although actual correlation coefficients were not provided), while none of these variables were associated with cognitive dysfunction.

Overall, results from this study revealed that patients undergoing chemotherapy treatment experience significant fatigue and menopausal symptoms. These side effects lead to an overall reduced quality of life, although neither fatigue nor menopausal symptoms appear to be a determining factor in chemotherapy-induced cognitive decline. The incidence of moderate to severe cognitive dysfunction was lower than that reported in the pilot study (Brezden et al., 2000) and was more consistent with that found in other studies (Schagen et al., 1999; van Dam et al., 1998). Fortunately, a one- and two-year follow-up was planned for this sample to better appreciate the time course of fatigue, menopausal symptoms, and cognitive decline (Fan et al., 2005).

At the one-year follow-up (from the time of first assessment), data were obtained for 91 breast cancer subjects and 81 controls (81 matched pairs), while at year two, 83 patients and 81 control subjects (73 matched pairs) were re-evaluated (Fan et al., 2005). Attrition was reasonable and mainly due to ineligibility (e.g., breast cancer recurrence), death, and withdrawal of consent. Moreover, there were no significant differences between those who completed follow-up assessments and those who did not on the primary factors of interest (overall classification of cognitive function as measured by the HSCS, fatigue, menopausal symptoms, and general quality of life), suggesting that any differences in outcome was probably not due to biases' in study participation. The test protocol remained intact between the initial and follow-up sessions, the only exception being the removal of the Conner's Continuous Performance Test given that it had failed to distinguish between groups at first assessment.

By first follow-up, all participants had completed adjuvant chemotherapy, the majority of whom had received either six cycles of CEF (63%) or four cycles of AC (19%). Adjuvant hormonal therapy (mostly tamoxifen) was provided to ER+ patients subsequent to

completion of chemotherapy treatment - 63% of patients at Year 1 and 67% of patients at Year 2.

Over the follow-up period, the proportion of breast cancer survivors in the moderate to severe range of cognitive dysfunction declined from 16% (Tchen et al., 2003; $p = .02$ across all categories of cognitive dysfunction) to 4.4% ($p = .03$ across all categories of cognitive dysfunction) at first follow-up, and to 3.8% ($p = .07$ across all categories of cognitive dysfunction) by year two as compared to controls. In the same categories, performance by the healthy volunteers during the same time frame was 5%, 3.6%, and 0%. The upward shift (improvement) in the proportion of healthy control participants with a moderate to severe classification was attributed to practice effects. While the effects of practice apply to both patients and controls, patients still performed somewhat worse than their healthy counterparts at year one (Fan et al., 2005).

There were no significant differences in HSCS scores between those participants treated with tamoxifen and those who were not. Additionally, while fatigue and menopausal symptoms also declined during the same time period, findings revealed that much like the first assessment, these factors and quality of life were strongly correlated with each other ($p < .0001$ in both cases) but not with cognitive test scores. While it is not possible to attribute a causal relationship based on correlation analyses, the results taken together are suggestive that the effects of chemotherapy may have had a negative effect on cognitive function. Interestingly, while this appears to be the case, it is noteworthy that by year two, there were essentially no differences between the groups in terms of the classification of cognitive dysfunction. This suggests that any cognitive dysfunction related to chemotherapy-induced cognitive decline is reversible and is consistent with the findings of Schagen, Muller, Boogerd, Rosenbrand et al. (2002).

A group of researchers from New Hampshire have contributed several studies to this research field; two papers are based on original data (Ahles, Tope, Furstenberg, Hann, & Mills, 1996; Ahles et al., 2002) and there are at least three qualitative review articles (Ahles & Saykin, 2001; Ahles & Saykin, 2002; Rugo & Ahles, 2003). In the first of these original reports, Ahles et al. (1996) evaluated cognitive function among patients with various hematologic disorders and breast cancer patients scheduled to receive high dose chemotherapy followed by autologous bone marrow transplantation. While findings revealed a decline in neuropsychological function, given obvious differences in the breast cancer group selected for such a treatment protocol, it is not reviewed here. Furthermore, in the various qualitative reviews evaluating cognitive function and early stage breast cancer treatment, this paper was omitted (e.g., Phillips & Bernhard, 2003).

In the second original report by the New Hampshire group, Ahles et al. (2002) investigated the cognitive functioning of long-term survivors of lymphoma and early stage breast cancer patients treated with standard chemotherapy ($n = 36$ and $n = 35$, respectively) compared to a group of patients treated with local surgery and/or radiation only (lymphoma, $n = 22$; breast cancer, $n = 35$). The majority of breast cancer patients received CMF or CAF. Across participants treated with chemotherapy, the median number of chemotherapy cycles was six, although there was a considerable range (minimum = 1, maximum = 17). Among the breast cancer groups, 37% of those treated with chemotherapy and 14% treated with surgery alone, received tamoxifen. All participants were assessed using a two-hour battery of standardized neuropsychological tests and completed self-report measures of cognitive problems, mood, fatigue, and psychological functioning, roughly 10 years after diagnosis. With the exception of the raw score data that were presented for each group, the results between breast cancer and lymphoma patients

were combined. While the amalgamation of these two cancer groups likely reduced the recruitment period and boosted power, it also provided for some confounds, most prominently related to the type of cancer and its differential treatment. Keeping in mind these constraints, this study has been included in qualitative and quantitative (e.g., Falletti et al., 2005; Morse et al., 2003) summaries of this literature, and as such, an analysis of the results is presented below.

Compared with published norms, performance among the different groups was generally within normal limits. Logistic regression analyses were performed with treatment (chemotherapy versus local therapy) and diagnosis (breast cancer versus lymphoma) as independent variables, nine cognitive domain scores (attention for vigilance and accuracy, attention and reaction time, verbal ability, verbal learning, verbal memory, visual memory, psychomotor function, motor function, and spatial ability) as dependent variables, and age and education as covariates. First, there was no effect of diagnosis suggesting that any effects due to type of cancer were minimal. There was, however, a significant treatment effect ($p < .01$) such that chemotherapy patients performed more poorly than their no-chemotherapy counterparts. Tasks measuring verbal memory (Logical Memory I [$p < .03$] and Logical Memory II [$p < .01$]) and psychomotor function (Digit Symbol subtest of the Wechsler Adult Intelligence Scale – Third edition [WAIS-III, Wechsler, 1997; $p < .02$]) were particularly affected. As seen in previous studies (e.g., Wefel, Lenzi, Theriault, Davis et al., 2004), there was no relationship between self-reported cognitive problems and neuropsychological scores. Similarly, no differences were reported between those who had or had not received hormonal treatment. A low but significant association between the number of cycles of chemotherapy received and neuropsychological domain deficits was also reported ($r = .31$, $p < .02$).

Additionally, Ahles et al. (2002) evaluated the frequency of low performance between the groups. Low performance was defined as scores within the lower quartile on at least four (of nine) cognitive domains. Thirty-nine percent of chemotherapy patients compared to 14% of controls ($p < .01$) scored within the lower quartile. To ensure that these results were not due to a somewhat arbitrary definition of low performance, the same criterion was applied to three and five cognitive domains. In all cases, the level of low performance was at least double that of the control group and always reached statistical significance at $p < .05$. Moreover, similar analyses revealed that this pattern was not influenced by type of cancer diagnosis. Of final note, these results were observed a full 10 years after the initial breast cancer diagnosis.

As part of a larger study investigating the reproductive health of women after breast cancer treatments, Castellon et al. (2004) evaluated the cognitive effects of adjuvant systemic therapy in a group of 53 stage 0, I, or II breast cancer patients treated with chemotherapy with or without tamoxifen ($n = 36$), or surgery alone ($n = 17$). A comparison group of 19 healthy, gender- and age-matched controls was also included. Overall, the sample was young (mean age = 47.8 years, $SD = 5.8$) and well-schooled (mean number of years of education = 16.5 years, $SD = 2.4$) with an estimated verbal IQ of 119 ($SD = 6.4$), as measured by the National Adult Reading Test (Blair & Spreen, 1989). There were no significant differences between the groups on these demographic characteristics.

All breast cancer participants had been diagnosed two to five years earlier. Forty-one percent of the experimental group had been treated with a CMF protocol, 38% with AC alone or with CMF, and the remaining 9% of the sample with an AC-taxane containing regimen. In addition to the standard regimens described, eight women received a high dose of chemotherapy (no other details were provided).

The neuropsychological assessment consisted of a two-hour battery of mostly common neuropsychological measures, organized according to the following cognitive areas: executive attention, psychomotor speed, reaction time, verbal fluency, verbal learning, verbal memory, visual memory, and visuospatial function. Additionally, a global score of all cognitive domains (Global Neurocognitive Performance) was also computed. Self-reported mood (Beck Depression Inventory - II; Beck, Steer, & Brown, 1996), anxiety (State-Trait Anxiety Inventory; Spielberger, Gorsuch & Lushene, 1971), fatigue (4-item energy/fatigue subscale of the Medical Outcomes Study Short-Form-36; Ware & Sherbourne, 1992), and perceived cognitive function (Cognitive Failures Questionnaire; Broadbent, Cooper, Fitzgerald, & Parkes, 1992) were also assessed. The control group endorsed significantly more anxious symptoms ($p = .01$), although results for both groups remained within normal limits. There were no significant differences on measures of mood or fatigue with group means well within the expected range.

Castellon et al. (2004) used traditional methods of analysis in the treatment of their data by way of a multivariate approach. Although the omnibus F was not reported, there was a significant main effect of group. They followed this up with univariate analyses that revealed that breast cancer participants who received adjuvant therapy scored significantly worse than breast cancer patients treated with surgery only on the cognitive domains of visual memory ($p = .01$), visuospatial function ($p = .005$), and verbal learning ($p = .03$). Four standardized measures were found to discriminate between groups with very large treatment effects and they were as follows: Block Design subtest of the WAIS-III (Cohen's $d = .90$), Rey-Osterreith Complex Figure Copy and Recall (Meyers & Meyers, 1995; $d = .58$ and $.80$ respectively), Visual Reproduction subtest of the WMS – Revised (Wechsler, 1987; $d = .81$), and California Verbal Learning Test, List B (Delis, Kramer, Kaplan, &

Ober, 1987; $d = .68$). With regard to Global Neurocognitive Performance, there was a statistically significant difference between breast cancer patients who received adjuvant treatment and those who did not ($p = .01$), although neither group was significantly different from healthy controls.

Exploratory analyses were conducted to determine the relative contribution of tamoxifen on cognitive dysfunction. A four-group multivariate analysis of variance (MANOVA) was conducted with the healthy control group and the breast cancer groups differentiated according to whether patients received chemotherapy and tamoxifen ($n = 18$), chemotherapy alone ($n = 18$), or surgery alone ($n = 17$). Once again, there was an overall significant main effect of group on the MANOVA. Follow-up pairwise comparisons showed that patients who received both chemotherapy and tamoxifen performed significantly worse than surgery alone patients on measures of verbal learning ($p = .005$), visual memory ($p = .009$), visuospatial function ($p = .002$). Between these two groups, a similar pattern of lower performance was also observed on the Global Neurocognitive Performance ($p = .02$). Patients treated with chemotherapy alone scored significantly lower than healthy controls on verbal fluency ($p = .001$) and compared to surgery alone patients, there were trends for poorer performance on visual memory ($p = .06$), verbal fluency ($p = .06$), and visuospatial function ($p = .07$).

The relationship between objective and subjective neuropsychological performance was in-line with previous reports (e.g., Ahles et al., 2002; van Dam et al., 1998). Among breast cancer patients, the correlations between the eight cognitive domains and self-reported cognitive failures were small and non-significant, while mood and anxiety were positively correlated with everyday cognitive lapses (r 's = .44 and .42, respectively, both

p's <.01). Among breast cancer patients, those who reported less energy were more likely to endorse cognitive complaints ($r = -.39$, $p < .05$).

Overall, results from this retrospective study suggest that chemotherapy either alone or in combination with tamoxifen exerts subtle but statistically significant cognitive compromise among breast cancer survivors up to five years past initial diagnosis. These differences could not be accounted for by self-reported mood, anxiety, or fatigue. This cognitive dysfunction could not be exclusively attributed to the effects of adjuvant hormonal treatment.

Without exception, the above retrospective studies have concluded that some women exposed to adjuvant chemotherapy for the treatment of early stage breast cancer are at increased risk to experience of cognitive loss. Donovan et al. (2005) marks the only retrospective study to provide an opposing view. While Scherwath et al. (2006) concluded that their results did support chemotherapy-induced cognitive decline, a consistent lack of significant findings with only weak trends appears to indicate otherwise. Each of these studies is reviewed below.

As part of a larger study evaluating quality of life during and after treatment for breast cancer, Donovan et al. (2005) recruited a sub-sample of 60 Stage 0, I, or II patients who underwent a standard chemotherapy schedule and radiation ($n = 60$) or radiation alone ($n = 83$). The majority of participants who received chemotherapy obtained AC (56%), while the remainder received AC-paclitaxel (17%), AC-docetaxel (10%), CMF (13%), or A-Taxotere (3%). About six months after completion of radiation treatment and on average 275 days ($SD = 43.0$ days) post-chemotherapy treatment, participants were administered a set of neuropsychological measures evaluating attention, complex cognition, language, and motor function. Additionally, participants answered questions related to cognitive

difficulties in everyday life, fatigue, and depression. Those who agreed to participate in the neuropsychological portion of the study were significantly more educated than those who did not ($p < .005$), possibly introducing a sampling bias. Among participating groups, there were also some differences; chemotherapy and radiation patients were significantly younger than their control counterparts, more likely to be pre-menopausal, and much less likely to be taking tamoxifen at the time of the assessment.

Prior to analyses, all neuropsychological test scores were standardized using norms based on age, education, or some combination of these. The investigators conducted a series of 13 ANOVAs with age and hormonal therapy status as covariates. Even before correcting for the increased likelihood of Type I errors, none of the ANOVAs met the .05 conventional criteria for statistical significance, with effect sizes ranging from $d = .00$ to .29. This is of considerable contrast to Castellon et al. (2004) who found large effect sizes of up to .80 or higher on three neuropsychological measures.

Donovan et al. (2005) defined cognitive impairment as a score of two standard deviations below published norms on any measure. According to this criterion, the prevalence of cognitive impairment in both groups was similar and low with a median number of impaired tests of 0.35 ($SD = .73$; range 0 - 4). Additionally, there were no significant differences regarding self-reports of cognitive complaints. While objective evidence suggested that cognitive impairment was a relatively infrequent occurrence, the overall sample rated the occurrence of cognitive problems as “frequently.”

In a recently published study, Scherwath et al. (2006) investigated the neuropsychological function of 23 breast cancer patients treated with standard dose adjuvant chemotherapy and 24 high risk breast cancer patients treated with stem-cell supported high dose chemotherapy, five years post-treatment. The standard dose

chemotherapy protocol was CMF. High dose participants received four cycles of EC and were subsequently randomized to receive either three cycles of standard dose CMF or high dose cyclophosphamide, thiotepa, and mitoxantrone, followed by autologous hematopoietic stem-cell support. A control group matched for age, education, and time since treatment consisted of stage I or II breast cancer patients' treated with surgery and radiation only (no chemotherapy). Almost half of the experimental groups and only about one-quarter of the control group were taking tamoxifen at the time of evaluation. There were no significant differences between the three groups with respect to age, education, estimated IQ, use of tamoxifen at assessment, or time since last treatment.

Participants were administered a two-hour battery of commonly used tests involving attention, memory, and executive functions. Eighteen test parameters were analyzed. Using criteria as set forth by the Compendium of Neuropsychological Tests (Spreeen & Strauss, 1998), the investigators defined cognitive impairment as scoring 1.5 SD below the mean of zero; this corresponds to a cutoff equal to or less than 8%. A global impairment score was also calculated for each individual via a tally of the number of measures in the impaired range. Breast cancer patients who scored below the fifth percentile on four or more measures were considered impaired in their global neuropsychological performance.

Even after controlling for multiplicity, compared to the standardization samples of the various tests, there were some unexpected differences in that one or more of the groups scored below expected limits on two measures and above expected limits on three others. While there was a trend for standard and high dose patients to score worse on a measure of selective attention and for standard dose patients to perform worse than control subjects on a letter fluency task ($p = .18$), these differences did not reach statistical significance. Similarly, the frequency of global impairment was not significantly different between the

groups. While these results are most similar to Donovan et al. (2005), the smaller than usual sample size calls into question the power to detect subtle differences.

Summary: Qualitative and quantitative reviews of the effects of adjuvant chemotherapy in breast cancer

A myriad of narrative reviews on this topic have been published in recent years (Table 6). Taken together, these qualitative reviews have expertly critiqued methodological limitations and speculated on the negative impact of possible neuropsychological deficits on everyday activities and work-related duties. While these summaries have acknowledged the increasing evidence in support of chemotherapy-induced cognitive loss, they have also tempered their conclusions due to insufficient prospective data, suggesting that any findings to date are preliminary in nature (Castellon, Silverman, & Ganz, 2005; Morse et al., 2003; Olin 2001; Phillips & Bernhard, 2003).

At present, the profile of neuropsychological deficits appears to be diffuse, spanning a broad range of functioning, including attention/concentration, working memory, short- and long-term memory, speed of processing, language, spatial ability, and motor function (Schagen, Muller, Boogerd, & van Dam, 2002; Castellon et al., 2005). However, performance appears to be generally within the normal range when compared to healthy standardization samples, indicating that the effects are subtle (Ahles & Saykin, 2002). While some investigators have used the term “clinical impairment” to describe a proportion of breast cancer patients meeting a specified criteria, given the subtle nature of these deficits, these patients would not normally be considered “impaired” in a clinical setting.

Table 6. List of qualitative review articles evaluating chemotherapy-induced cognitive decline in early stage breast cancer.

Ahles, T.A., & Saykin, A. (2001). Cognitive effects of standard-dose chemotherapy in patients with cancer. *Cancer Investigation*, 19, 812-820.

Ahles, T.A., & Saykin, A.J. (2002). Breast cancer chemotherapy-related cognitive dysfunction. *Clinical Breast Cancer Supplement*, 3, S84-S90.

Barton, D., & Loprinzi, C. (2002). Novel approaches to preventing chemotherapy-induced cognitive dysfunction in breast cancer: The art of the possible. *Clinical Breast Cancer*, 3 (Suppl. 3), S121-127.

Bender, C.M., Paraska, K.K., Sereika, S.M., Ryan, C.M., & Berga, S.L. (2001). Cognitive function and reproductive hormones in adjuvant therapy for breast cancer: A critical review. *Journal of Pain and Symptom Management*, 21, 407-424.

Castellon, S.A., Silverman, D.H.S., & Ganz, P.A. (2005). Breast cancer treatment and cognitive functioning: Current status and future challenges in assessment. *Breast Cancer Research and Treatment*, 92, 199-206.

Freeman, J.R., & Broshek, D.K. (2002). Assessing cognitive dysfunction in breast cancer – What are the tools? *Clinical Breast Cancer*, 3, (Suppl. 3), S91-99.

Matsuda, T., Takayama, T., Tashiro, M., Nakamura, Y., Ohashi, Y., & Shimoizuma, K. (2005). Mild cognitive impairment after adjuvant chemotherapy in breast cancer patients – evaluation of appropriate research design and methodology to measure symptoms. *Breast Cancer*, 12, 279-87.

Morse, R., Rodgers, J., Verrill, M., & Kendell, K. (2003). Neuropsychological function following systemic treatment in women treated for breast cancer: A review. *European Journal of Cancer*, 39, 2288-2297.

O'Shaughnessy, J.A. (2003a). Chemotherapy-induced cognitive dysfunction: A clearer picture. *Clinical Breast Cancer*, 4(Suppl. 2), S89-S94.

O'Shaughnessy, J.A. (2003b). Chemotherapy-related cognitive dysfunction in breast cancer. *Seminars in Oncology Nursing*, 19, (Suppl. 2), 17-24.

Olin, J.J. (2001). Cognitive function after systemic therapy for breast cancer. *Oncology*, 15(5), 613-624.

Phillips, K.-A., & Bernhard, J. (2003). Adjuvant breast cancer treatment and cognitive function: Current knowledge and research directions. *Journal of the National Cancer*

Institute, 95, 190-197.

Rugo, H.S., & Ahles, T. (2003). The impact of adjuvant therapy for breast cancer on cognitive function: Current evidence and directions for research. *Seminars in Oncology*, 30, 749-762.

Saykin, A.J., Ahles, T.A., & McDonald, B.C. (2003). Mechanisms of chemotherapy-induced cognitive disorders: Neuropsychological, pathophysiological, and neuroimaging perspectives. *Seminars in Clinical Neuropsychiatry*, 8, 201-216.

Schagen, S.B., Muller, M.J., Boogerd, W., & van Dam, F.S.A.M. (2002). Cognitive dysfunction and chemotherapy: Neuropsychological findings in perspective. *Clinical Breast Cancer*, 3, (Suppl.3), S100-S108.

Wefel, J.S., Kayl, A.E., & Meyers, C.A. (2004). Neuropsychological dysfunction associated with cancer and cancer therapies: A conceptual review of an emerging target. *British Journal of Cancer*, 90, 1691-1696.

Additionally, not all breast cancer patients are at equal risk for cognitive decline (Ahles & Saykin, 2001); a subgroup of approximately 30% appears to be most vulnerable (Castellon et al., 2004; Schagen et al., 1999; Shilling et al., 2005; van Dam et al., 1998). This suggests that there are individual or treatment-related factors that may be influencing the outcome (Olin, 2001; Rugo & Ahles, 2003). The studies previously described evaluated a broad range of potential contributing factors, including disease severity, hormonal status, impact of co-medications, psychological functioning (e.g., depressive and anxious symptomatology, fatigue), and individual differences in age, education, and IQ. These variables do not appear to be driving the relationship between adjuvant chemotherapy and cognitive decline in breast cancer patients nor is there any evidence to suggest that any of these factors contribute significantly to a cognitive vulnerability.

While there is some support for a dose-dependent effect between chemotherapy and cognitive decline (van Dam et al., 1998), the lack of such a definitive relationship has led some to hypothesize that the observed deficits may be due to a substance-dependent state (e.g., Scherwath et al., 1996). Chemotherapy agents and regimens are unique and thus it is expected that different agents or regimens confer different effects (Anderson-Hanley et al., 2003; Wefel, Kayl, & Meyers, 2004). Methotrexate has been targeted as a potential source of concern; however it is known to cross the BBB only poorly (Cancer Care Ontario Formulary, 2004/2005) and results in central nervous toxicity only after high-dose administration (Tuxen & Hansen, 1994 as cited in Kreukels et al., 2005). In contrast, fluorouracil and 5-FU readily cross the BBB and are an important component in commonly prescribed anthracycline-based regimens (Saykin, Ahles, & McDonald, 2003).

With respect to the impact of adjuvant hormonal treatment, some investigators more carefully controlled for this potential extraneous factor than others. Given that hormonal treatment is thought to cross the BBB (Kreukels et al., 2005), it may be responsible for some of the observed effects in cognitive deterioration.

While narrative reviews have been helpful in summarizing the existing literature, they are unable to quantify the magnitude of any observed neuropsychological deficits (Anderson-Hanley et al., 2003). Meta-analytic tools are able to perform such a function and have the added advantage of being able to pool the results from several small studies. As a first effort in quantifying the neuropsychological effects of cancer treatment (e.g., chemotherapy and biologic treatments), Anderson-Hanley et al. (2003) combined the results from 30 studies across different types of cancer (e.g., breast, bowel, colorectal, ovarian, lung). They found small to medium effect sizes in most cognitive domains with

particularly adverse effects on executive function and verbal memory. These results, although of interest, are not specific to the effects of breast cancer per se.

Aside from our own meta-analysis of these findings (Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006), Falletti et al. (2005) recently published a meta-analysis of the cognitive effects of adjuvant chemotherapy in early stage breast cancer. These investigators combined the results from five retrospective studies (Ahles et al., 2002; Castellon et al., 2004; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995) and separately analyzed a single prospective design (Wefel, Lenzi, Theriault, Davis et al., 2004). Neuropsychological measures were classified according to the following six cognitive domains (effect sizes for the retrospective studies appear in brackets): attention (-.03), executive function (-.18), language (-.41), memory (-.26), motor function (-.51), memory (-.26), and spatial ability (-.48). With the exception of attention, the magnitude of impairment was small to moderate, relatively consistent, and thus suggestive of global or diffuse effects. The size of the impairment diminished as the time since treatment increased, lending support for the notion that the observed effects are at the very least, partially reversible. In the prospective design, effect sizes ranged from a low of .11 to a high of 1.09 in the short-term assessment and diminished at second follow-up.

In summary, there is growing support from both prospective and retrospective studies to suggest that adjuvant chemotherapy for the treatment of early stage breast cancer results in subtle cognitive loss. These effects have been found up to 10 years past the initial diagnosis. Nevertheless, follow-up studies and results by Wefel, Lenzi, Theriault, Davis et al. (2004) suggest that the observed effects are at least partially reversible. While the reversibility of this phenomenon remains controversial, it does highlight the need to document the incidence of chemotherapy-induced neuropsychological decline shortly after

treatment in order to best appreciate any long-term consequences. Using a prospective design, this was a main focus of Study 2.

Specific factors that may influence neuropsychological function

Premorbid mental ability and education

High overall IQ and education are associated with better performance on neuropsychological tests (Howieson, Loring, & Hannay, 2004). While tests of verbal abilities are well-known to be sensitive to education effects, improved performance as a result of schooling may also occur among tasks seemingly unaffected by training (e.g., Digit Span; Howieson et al., 2004). Additionally, persons with a better education and overall IQ are more likely to benefit from practice effects (Rapport et al., 1997).

With respect to trauma to the brain, there is supporting evidence to show that higher education and overall IQ may buffer against the cognitive loss associated with an insult to the brain (Howieson et al., 2004). This is commonly referred to as the cognitive reserve hypothesis (Stern, 2002). In so far as one considers adjuvant chemotherapy to be a type of trauma or insult to the brain (Rugo & Ahles, 2003), the potential for some breast cancer patients to withstand the iatrogenic effects of chemotherapy is of importance (Ahles & Saykin, 2001).

The majority of volunteers in the current studies have been generally better educated than the general population. In the most extreme case, in Wieneke & Dienst's (1995) sample of 28 early stage breast cancer patients, 93% had some university education, with almost one-third of those having had graduate training. Although the cognitive reserve hypothesis has not been formally tested in this population (Ahles & Saykin, 2001),

it does propose that any findings of cognitive decline in these studies are likely underestimated given that most of the samples have had greater educational backgrounds than the general population. In order to best control for this factor, Rugo & Ahles (2003) recommended that participants be matched for education and IQ or less desirably, use these variables as covariates in any statistical procedures.

Issue of pre-existing neuropsychological problems. It has been suggested that neuropsychological decline associated with adjuvant chemotherapy treatment may be the consequence of pre-existing neuropsychological difficulties (Cimprich et al., 2005; Schagen et al., 2002; Wefel, Lenzi, Theriault, Buzdar et al., 2004). There are many factors that may contribute to atypical baseline performance on neuropsychological measures in newly diagnosed breast cancer patients, including mood disturbance related to the initial diagnosis, type of surgery and general anesthetic, history of hormone replacement therapy, and hormonal status (Fan et al., 2005; Wefel, Lenzi, Theriault, Buzdar et al., 2004). The issue of pre-existing neuropsychological difficulties was the focus of two recently published papers.

The research group who published the first prospective investigation of chemotherapy-induced cognitive decline associated with breast cancer (Wefel, Lenzi, Theriault, Davis et al., 2004) combined results from three different study protocols to investigate whether pre-existing cognitive problems was a mediating factor in chemotherapy-induced neuropsychological decline (Wefel, Lenzi, Theriault, Buzdar et al., 2004). The sample consisted of 84 women who were administered standardized neuropsychological tests a mean of 53 days post-surgery (SD=39.8 days). Given a heterogeneity in test protocols, participants were administered a minimum of 5 and up to 14

standardized measures. The tests took anywhere from 40 to 120 minutes to complete. The study cohort also filled out the BDI or BDI-II, the State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), Beck Anxiety Inventory (Beck & Steer, 1997), and the Minnesota Multiphasic Personality Inventory (Hathaway & McKinley, 1970).

Raw test scores were standardized (z-scores) and compared to age and/or education-stratified normative data. Statistical significance was set at .01 to correct for multiplicity of test measurement. Cognitive impairment was defined as scoring below 1.5 SD on at least two measures or below 2 SD on a single measure; this is likely to occur 7% and 2% respectively of the time in healthy individuals (Hannay & Lezak, 2004; Wefel, Lenzi, Theriault, Buzdar, et al., 2004). Prior to the initiation of adjuvant chemotherapy, 35% of the sample ($p < .001$) was classified as cognitively impaired, with verbal learning and verbal memory especially affected. While the classification of cognitive impairment was unaffected by age or education, persons who were psychologically distressed were significantly more likely to be cognitively impaired ($p = .002$). This marks the first study to demonstrate a significant association between affective distress and objective cognitive impairment, although this result seemed to be driven in part by a single relationship between anxiety (State-Trait Anxiety Inventory) and performance on Trails B ($r = -.42$, $p < .01$).

More recently, Cimprich et al. (2005) investigated pre-treatment factors related to attentional capacity in a large sample of newly diagnosed early stage breast cancer patients ($N = 186$). The mean age of the group was 55 ($SD = .84$), the majority of whom were post-menopausal (65%). Unlike the study by Wefel, Lenzi, Theriault, Buzdar et al. (2004), this

sample was tested about 18 days prior to surgery, thus eliminating any concerns due to type of surgery or ill-effects of general anesthetic.

The neuropsychological assessment was short and limited to three measures of attentional capacity: Digit Span (Forward and Backward), the Trail-making Test, and a lesser known test of short-term memory and retention of information, Three Shapes and Three Words (Mesulam, 1985). Based on these measures, a Total Attention Score was also computed. Distress and mood were measured using the Symptom Distress Scale (McCorkle & Young, 1978) and the Profile of Mood States-Short form (McNair et al., 1992), respectively. Self-reported effectiveness in cognitive functioning was estimated using the Attentional Functional Index (Cimprich, 1992), a validated tool that asks respondents to rate, among other items, their level of efficacy regarding the planning of daily activities, initiation, and maintaining a train of thought, etc. At pre-treatment, breast cancer patients showed a low-to-moderate level of symptom distress. A low level of mood distress was also noted on the POMS-Short form, although one-quarter of the group had moderate-to-high distress.

The investigators concluded that performance on the attention tasks was generally within normal limits. Using the Total Attention Score as the dependent variable, a multiple regression analysis was carried out to test for predictors of cognitive functioning. Among age, years of education, menopausal status, co-morbid health conditions (e.g., diabetes, hypertension, heart disease), and overall scores on the Symptom Distress Scale and POMS-Short form, only age and education were found to be significant predictors of overall attentional abilities. This is not surprising given that two of the most important factors in determining neuropsychological performance are age and education (Howieson et al., 2004). Assuming that prior to the initiation of any kind of treatment, the cognitive function

of newly diagnosed breast cancer patients is within the normal range, this assumption is in keeping with the said results. Clearly however, this study is limited by the narrow selection of neuropsychological measures.

Overall, findings from pre-treatment assessments of newly diagnosed breast cancer patients are equivocal. This underscores the importance of baseline neuropsychological evaluation to ensure that any cognitive decline can be appropriately attributed to the effects of chemotherapy and not other causes.

Psychological factors

The psychological and psychiatric morbidity associated with a breast cancer diagnosis and treatment has been well-studied, but with equivocal findings. While there is some support to show that elevated levels of anxious and depressive symptoms among breast cancer patients at the time of diagnosis and throughout treatment and recovery (Del Mastro et al., 2002; Epping-Jordan et al., 1999; Woodward & Webb, 2001) are of sufficient severity to reach the criterion for a mood or anxiety disorder (Kissane, Grabsch, Love, Clarke, Bloch, & Smith, 2004), others suggest that the rates of psychological distress are in-line with the general population (Compas & Luecken, 2002; Spijker et al., 1997). In a review of psychological adjustment to breast cancer, Compas & Luecken (2002) concluded that distress is at its peak at around the time of diagnosis and declines over time, with only a minority of patients experiencing heightened levels of anxiety or depression many years after diagnosis. The patient characteristics robustly associated with a good psychological adjustment to breast cancer include age over 50 years and optimism (Compas & Luecken, 2002; Compas, Stoll, Thomsen, Oppedisano, Epping-Jordan, & Krag, 1999; Spijker et al.,

1997). Surprisingly, while disease severity and type of treatment have not been typically associated with psychological distress (Compas & Luecken, 2002; Kissane et al., 2004), a higher dose-intensity chemotherapy regimen (e.g., every 14 instead of 21 days) was related to an acute increase in psychological distress (Del Mastro et al., 2002).

In terms of neuropsychological decline, depressive and anxious symptoms have been associated with reduced speed of processing, mild attentional difficulties, verbal and visual memory problems, reduced verbal fluency and mental flexibility, and visuospatial difficulties (Cimprich & Ronis, 2001; Howieson et al., 2004). Studies directly involved in the evaluation of chemotherapy-induced cognitive decline have been cognizant of these potential effects and have either excluded patients on the basis of current or past psychiatric history and/or were careful to include tests to measure these symptoms (Rugo & Ahles, 2003). With the exception of Wefel, Lenzi, Theriault, Buzdar et al., 2004), none of the studies to date have found a relationship between depression/anxiety and the cognitive decline observed in breast cancer patients.

Fatigue

Treatment-induced fatigue is a common and distressing aspect of breast cancer and is associated with a decrease in daily functioning (Beisecker et al., 1997; de Jong, Candel, Schouten, Abu-Saad, & Courtens, 2004) and overall reduced quality of life (Bower, Ganz, Desmond, Rowland, Meyerowitz, & Belin, 2000). Cancer-related fatigue is distinct from “everyday” fatigue by virtue of its severity and persistence in the face of ample relaxation and sleep (Young & White, 2006). Levels of fatigue have been found to vary according to the type and order of cancer treatment. For instance, a greater level of fatigue has been

reported among those treated with doxorubicin as compared to CMF and is more severe among women treated with a combination of chemotherapy and radiation versus radiation alone (Donovan et al., 2004; de Jong et al., 2004). Adding to its complexity, the phenomenon of fatigue is a difficult-to-define, multidimensional feeling that incorporates elements of cognitive (e.g., attention and concentration), physical (e.g., low energy), and psychological or affective states (e.g., reduced motivation and anhedonia; Haghighat, Akbari, Holakouei, Rahimi, & Montazeri, 2003). For many breast cancer patients, fatigue persists for many months or even years beyond the treatment period, this despite indications of successful outcome to therapy (Bower et al., 2006). Fatigue induced by treatment for breast cancer has been shown to be indistinguishable from fatigue related to psychological symptoms such as depression (Bennett, Goldstein, Lloyd, Davenport, & Hickie, 2004).

Fatigue has been associated with neuropsychological decline in patients suffering from chronic fatigue syndrome and as such has been identified as a possible mediator in chemotherapy-induced cognitive decline (Servaes, Verhagen, & Bleijenberg, 2002; Tchen et al., 2003). In a systematic review of the neuropsychological effects of chronic fatigue syndrome, Michiels and Cluydts (2001) concluded that while there was no overwhelming evidence to suggest that chronic fatigue syndrome results in reduced cognitive efficiency, there was some evidence showing difficulties with processing speed, working memory, and learning.

As summarized earlier, Tchen et al. (2003) directly investigated the possible influence of fatigue as a potential factor in chemotherapy-induced cognitive decline and found no such relationship. The impact of fatigue was also evaluated by Servaes et al. (2002). Using only two standardized measures of cognitive function, Servaes et al. (2002)

investigated the impact of fatigue on neuropsychological function among a group of long-term breast cancer survivors (mean of 2.5 years post-treatment) differentiated according to whether they demonstrated severe fatigue on self-report ($n = 57$) or not ($n = 93$).

Additionally, an age-matched group of healthy women ($n = 78$) was recruited to serve as the comparison group. There were no group differences on age or education. The severely fatigued cohort was more likely to receive partial disability benefits. Performance among the three groups was similar on the Digit Symbol subtest of the WAIS, a measure of attention and concentration. However, on a task of processing speed, the severely fatigued group performed significantly worse when compared to control subjects only (p 's ranged from .001 to .009). No differences in performance between the groups could be attributed to type of treatment (e.g., no adjuvant treatment versus adjuvant treatment). Moreover, although education did not differ between the groups, data regarding IQ was not gathered and as such may have possibly influenced group differences.

While depression and anxiety have been assessed in most studies evaluating cognitive decline due to adjuvant chemotherapy, fatigue is one potential confound that has been evaluated far less (Ahles & Saykin, 2001). Among those studies that measured fatigue in some capacity, none found a subsequent link to cognitive decline as a result of adjuvant chemotherapy (Castellon et al., 2004; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998). In the breast cancer population, fatigue has been shown to be highly related to psychological distress (Bennett et al., 2004; Bower et al., 2000; de Jong, Candel, Schouten, Abu-Saad, & Courtens, 2005; Haghighat et al., 2003) and there is little evidence to support the hypothesis that cognitive decline in breast cancer patients treated with adjuvant chemotherapy is secondary to a fatigue-induced state. Nevertheless, given that

fatigue can fluctuate over time, fatigue should continue to be measured in this context (Ahles & Saykin, 2001).

Genetic factors

It is known that the $\epsilon 4$ allele of the apolipoprotein gene (APOE gene) hinders the ability of the brain to recuperate from neuronal injury (Small, Rosnick, Fratiglioni, & Backman, 2004), and thus provides a genetic basis for a predisposition to cognitive recovery from insult to the brain, either in the form of physical or pharmacological trauma. This genetic marker is found in approximately 14% of the general population (Small et al., 2004) and has been related to neuropsychological decline in Alzheimer's disease (Small et al., 2004), poorer outcome following an acute neurologic event (e.g., traumatic brain injury, hemorrhagic stroke, and subarachnoid hemorrhage; Waters & Nicoll, 2005), and reduced cognitive performance in healthy aging (Small et al., 2004).

To investigate whether such a genetic marker contributes to the vulnerability in what appears to be a subgroup of the breast cancer population, Ahles et al. (2003) recruited a sample of breast cancer ($n=51$) and lymphoma patients ($n=29$), previously treated with chemotherapy some 8.8 years ($SD=4.3$) prior to study enrolment. The cohort was subdivided on the basis of the presence (21%) or absence (79%) of the APOE gene. There were no significant differences between any relevant demographic or psychological factors between the two groups. All participants completed a two-hour battery of usual neuropsychological measures. While performance among the major cognitive domains was within the normal range for both groups, compared to participants without the APOE gene, carriers of the APOE gene showed significantly poorer performance in visual memory

($p < .03$) and spatial tasks ($p < .05$), with a trend for lower performance in psychomotor functioning ($p < .08$). These results lend some support to the notion that the APOE gene may serve as a genetic marker for increased vulnerability to chemotherapy-induced cognitive decline and marks one of the first studies of its kind to address the mechanisms underlying specific vulnerabilities.

Estrogen and neuropsychological function

Given the rich concentration of estrogen receptors in several neural structures, there is a growing interest in evaluating the effects of estrogen, either its provision (e.g., hormone/estrogen replacement therapy) or its deprivation (e.g., tamoxifen or arimidex) in the female brain. Influential evidence from the Women's Health Initiative Memory Study (a randomized, placebo-controlled clinical trial of more than 7,000 participants), suggests that the extended use hormone replacement therapy (HRT) does not provide a neuroprotective effect against mild cognitive impairment nor dementia (Shumaker et al., 2004). These data however, are limited to women 65 years and older; the impact of HRT on younger, newly menopausal women is much more controversial (Howell & Cuzick, 2005; Sherwin, 2005). Given that HRT is contraindicated to breast cancer treatment, many participants in the main studies reviewed had not taken HRT for some time or were otherwise excluded due to concerns that it may influence cognitive function.

In the adjuvant setting, the cognitive effects of estrogen deprivation have been reviewed by a few, mostly observational studies. Small declines in the areas of semantic and verbal memory and speed of information processing have been reported (Eberling, Wu, Tong-Turnbeaugh & Jagust, 2004; Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004;

Paganini-Hill & Clark, 2000; Shilling, Jenkins, Fallowfield, & Howell, 2003) but because results are not based on stringent clinical trials, findings are considered preliminary. In a review of chemotherapy-induced cognitive decline in early stage breast cancer, Rugo & Ahles (2003) suggested that there was not sufficient evidence to conclude that the long-term use of hormonal treatment has a negative impact on cognition. Nevertheless, it is important to distinguish any deleterious effects on neuropsychological performance attributed to adjuvant chemotherapy from that related to hormonal treatment.

Hormonal changes associated with an accelerated menopause have also been posited as a potential source of bias related to the impact of adjuvant chemotherapy on neuropsychological status. While the effect of chemotherapy-induced menopause has been overlooked in many studies, Tchen et al. (2003) directly investigated this concern and observed no relationship between accelerated menopause and classification of cognitive dysfunction as measured by the HSCS.

Overall, the effect of estrogen deprivation on cognitive function is unclear. While reports of decline have been limited to memory and speed of processing domains, the effects of adjuvant chemotherapy on neuropsychological function appear to be more global in nature and therefore cannot be solely attributed to any potential bias associated with hormonal treatment (Olin, 2001).

Co-medications

Medical complications due to treatment with adjuvant chemotherapy are often managed with medications from varying drug classes including antiemetics, antibiotics, steroids, immunosuppressive agents, and drugs to treat pain. While these medications improve the tolerability and hence completion of treatment, some drugs also cross the BBB

and may exacerbate chemotherapy-induced cognitive dysfunction (Schagen et al., 2002; Wefel, Kayl, & Meyers, 2004). Some studies have tried to minimize such effects through direct manipulation of experimental design (e.g., Wefel, Lenzi, Theriault, Davis et al. [2004] administered cognitive tests three weeks after treatment with antiemetics) or review of medical charts for any medications before, during, or after treatment that could have seriously influenced cognitive performance. Although the majority of studies previously reviewed carried out at least a cursory review of medical charts, the breadth and complexity of medication effects on neuropsychological function makes this task difficult.

Overview of thesis articles

As mentioned, this thesis comprises two separate but related studies. Study 1 is a meta-analysis of existing data in the field and Study 2 employs original data to better understand the relationship between adjuvant chemotherapy and early stage breast cancer. A statement regarding contributions of collaborators and co-authors can be found in Appendix A.

Study 1

The purpose of this study was to conduct a meta-analysis in order to estimate the size of the cognitive deficit associated with adjuvant chemotherapy treatment in early stage breast cancer. The following seven studies were included in the meta-analysis: Ahles et al. (2002), Brezden et al. (2000), Castellon et al. (2004), Schagen et al. (1999), van Dam et al. (1999), Wefel, Lenzi, Theriault, Davis et al. (2004), and Wieneke & Dienst (1995).

Cognitive domains were separated into eight categories consisting of simple attention, working memory, short-term memory, long-term memory, speed of processing, language, spatial abilities, and motor abilities. The selection of a more expansive list of cognitive domains (e.g., differentiation of simple attention and working memory) was in an effort to identify any domain-specific cognitive deficits. Small to medium effect sizes were observed across each of the cognitive domains and similar to the findings by Falletti et al. (2005) were indicative of subtle, diffuse brain injury.

Study 2

Using a prospective methodology, this study was designed to examine the short-term neuropsychological effects of adjuvant chemotherapy in newly diagnosed early stage breast cancer patients. The experimental group consisted of 61 stage I, II, or IIIA breast cancer patients scheduled to receive standard dose adjuvant chemotherapy with or without adjuvant hormonal treatment. To control for the emotional distress of a cancer diagnosis and to some extent the effects of disease, the comparison group was composed of 51 newly diagnosed stage I or II breast cancer patients scheduled to receive adjuvant hormonal therapy only (most participants received either tamoxifen or arimidex). To reduce the potential confounds due to the variability in hormonal status and age-related cognitive decline, only women (at the time of recruitment) who were post-menopausal and not older than 65 years of age (with the exception of one participant who was 66 years old) were eligible to participate in the study. Finally, a small group of non-cancer, healthy controls ($n = 28$) were also included to gauge the extent of practice effects associated with repeated, neuropsychological assessment.

This study was a collaborative effort between the University of Ottawa, the Ottawa Hospital, and The Ottawa Hospital Regional Cancer Center. Ethics approval, yearly renewals to continue this project (e.g., Appendix B), and any associated advertising materials (Appendix C) were approved by The Ottawa Hospital Research Ethics Board. Ethics approval from the University of Ottawa was deemed unnecessary given that participants were not recruited nor tested at this site (Lise Frigault, personal communication, June 5, 2001). Written informed consent was obtained from all participants (Appendix D). The next sections broadly describe the selection of neuropsychological measures, timeframe for recruitment and data collection, and a brief overview of analyses selected for use.

Selection of neuropsychological measures and analyses. A comprehensive battery of standardized neuropsychological tests designed to assess each of the main functional areas was included. These standardized tests are commonly employed in clinical neuropsychological settings. Appendix E provides a brief overview of these measures, including validity and reliability data. The BDI-II was administered to assess depressive symptomatology and the POMS was included to gauge the extent of anxious and depressive symptoms, as well as the impact of fatigue on any cognitive deficits. A demographic and past medical history questionnaire was specifically developed for the current study (Appendix F). Following consent for medical release of information (Appendix G), medical charts were reviewed for details pertaining to participants' diagnosis and treatment (Appendix H).

All participants received a baseline assessment of psychological functioning and neuropsychological functioning prior to the start of adjuvant treatment, thus permitting the

cognitive effects of chemotherapy to be disentangled from any pre-existing differences in cognitive function between groups. All tests and questionnaires were re-administered following completion of the last cycle of chemotherapy, approximately four to five months following baseline evaluation in the experimental group, or at an equivalent time point in the adjuvant hormonal therapy group and healthy control groups. The order of test/questionnaire administration can be found in Appendix I. This order was selected to begin and end the testing session with relatively easy tests to reduce participant discouragement and to ensure that there was the appropriate amount of time between tests with a delayed component. Following recommendations by the WMS-III manual, tests were administered in the same order (Wechsler, 1998). The complete assessment took approximately three hours. Participant recruitment took place between February 2002 and February 2005. Data collection for the short-term evaluation was complete in November 2005.

The Statistical Package for the Social Sciences (version 13.0) was used for all data analyses. Mixed design ANOVA or analysis of covariance (ANCOVA) was used to examine the effects of group, test session, and their interaction on the raw scores from the neuropsychological measures, BDI-II, and the POMS subscales. However, given that group means are not informative about individual cognitive decline, a standardized-regression based (SRB) approach was also used to assess individual cognitive change (McSweeney, Naugle, Chelune, and Luders, 1993; Sawrie, Marson, Boothe, & Harrell, 1999). While other methods have been employed in this research domain (e.g., variations of the reliable change index; Shilling et al., 2005), we selected the SRB approach because it allows for inclusion of moderator variables and comparisons across measures, while accounting for practice effects and regression-to-the-mean. The SRB method uses the

test/retest scores of a reference group (either the adjuvant hormonal group or healthy controls in this case) to develop a regression equation that predicts retest scores. The difference between the predicted and obtained retest scores, divided by the standard error of the estimate, yields a standardized change score that reflects the direction and magnitude of change. The SRB change scores were calculated for each subject on each dependent variable.

STUDY 1

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**A Meta-analysis of the Neuropsychological Effects of Adjuvant Chemotherapy
Treatment in Women Treated for Breast Cancer**

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ABSTRACT

Given the improvement in mortality rates associated with breast cancer, the importance of understanding the long-term neuropsychological consequences of chemotherapy is becoming increasingly vital. This study applies meta-analytic techniques to the scant literature on the relationship between contemporary adjuvant chemotherapy treatment for breast cancer and cognitive dysfunction as examined through neuropsychological indices. Seven studies (involving more than 300 participants) were selected from over 200 potential articles, based on three inclusion criteria - presence of breast cancer, administration of chemotherapy treatment, and use of neuropsychological tests. From these, nine treatment-control comparisons were used to generate 129 *Hedge's d* effect sizes across the cognitive domains of simple attention, working memory, short- and long-term memory, speed of processing, language, spatial abilities, and motor function. Small to medium cumulative effect sizes, showing diminished cognitive function for chemotherapy treatment groups compared to control groups, were obtained for each of the eight cognitive domains. Overall, these results suggest that women who undergo adjuvant chemotherapy as treatment for breast cancer may experience subtle yet consequential cognitive decline.

INTRODUCTION

This report describes the application of meta-analytic techniques to studies dealing with the long-term cognitive effects associated with chemotherapy in women diagnosed with breast cancer. The rates of breast cancer are steadily increasing in most advanced industrialized countries and this form of cancer is now ranked as the third most common in the world (Pheby, 2001). Despite these alarming statistics, breast cancer is curable, largely due to earlier detection and more aggressive treatments. Even in women diagnosed with advanced stage breast cancer, the survival rate is 15% (Gralow, 1999), and return to pre-cancer lifestyle is becoming more achievable.

One common phenomenon experienced by individuals who have undergone conventional adjuvant chemotherapy for breast cancer is cognitive decline (Ahles et al., 2002; Brezden et al., 2000; Castellon et al., 2004; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis et al., 2004; Wieneke & Dienst, 1995). The neuropsychological sequelae typically include memory deficits and reduced concentration, and may be evident years after treatment (Ahles et al., 2002; Schagen et al., 1999). It has been suggested that these changes are a consequence of chemotherapy-related neurotoxicity. Computed tomographic scanning and magnetic resonance imaging have revealed structural cerebral damage in patients exposed to various chemotherapeutic and combined chemotherapy/radiation treatment regimens, with evidence that white matter is especially compromised (Asato et al., 1992; Lee, Nauert, & Glass, 1986; Meyers, Scheibel, & Forman, 1991; Moore, Packer, Karl, & Bleyer, 1994; Okeda et al., 1984). The pathophysiology of cognitive dysfunction induced by adjuvant chemotherapy treatments is

unknown. Possible mechanisms include direct or indirect chemical toxicity to neurons or other non-neuronal elements in the central nervous system, oxidative damage, inflammation, and destructive autoimmune responses (Barton & Loprinzi, 2002).

Toxicity to major organs as well as endocrine systems can also indirectly affect brain function (Koch Nogueira et al., 1998; Loeschner et al., 1989; Marina, 1997; Schwartz, 1995; Silberfarb, 1983). For example, there is substantial evidence that estrogen plays a role in maintaining normal memory function (Sherwin, 1997). Among women receiving chemotherapy, destruction of the ovaries, with ensuing changes in estradiol, is not an uncommon occurrence (Loeschner et al., 1989; Maraveyas & Mansi, 2000), and may explain some of the associated cognitive changes. Brain function may also be hampered by anemia and ensuing fatigue, a common symptom of chemotherapy (Ludwig & Strasser, 2001).

While cognitive complaints are frequent following chemotherapy treatment, there has been little systematic research on this phenomenon. Moreover, due to methodological problems such as insufficient sample sizes, lack of uniformity among samples, lack of control for primary disease-related cognitive changes, the effects of anxiety and depression, and the confounding effects of other adjuvant treatments such as tamoxifen, it has been difficult to conclude that cognitive dysfunction in treated breast cancer patients is directly related to chemotherapy. The lack of baseline measures of cognitive functioning is another limitation of the extant studies on this subject and could apply to any study using retrospective data. For example, Meyers et al., (1995) found that, in patients with small cell lung cancer, cognitive deficits were present *before* patients were exposed to

chemoradiation (perhaps reflecting paraneoplastic phenomena) that, in the absence of baseline testing, may well have been construed as treatment effects. The preliminary results from a prospective longitudinal study being carried out by our group indicate that breast cancer patients are not inferior to age-matched standardization samples on any of the neuropsychological measures used prior to their exposure to adjuvant systemic therapy (Stewart, Collins, Bielajew & Tomiak, 2003). Nonetheless, one cannot conclude that pre-existing differences do not exist without baseline tests.

Description of studies included in the meta-analysis

The strategy used in this paper is to include all studies that provided neuropsychological data in breast cancer patients treated with adjuvant chemotherapy. In the earliest of these, Wieneke and Dienst (1995) found that, at 3 and 18 months post-chemotherapy treatment, breast cancer patients scored at least one standard deviation beneath both their own estimated premorbid IQ scores and published norms in most cognitive domains assessed. Seventy-five percent of the sample was moderately impaired (i.e., scored at least two standard deviations below the normative mean on at least one neuropsychological measure). Moreover, the majority of participants showing moderate decline received cyclophosphamide, methotrexate, fluorouracil (CMF) treatment, suggesting an association between the type of chemotherapy regimen and cognitive deficits. Subsequently, two studies from The Netherlands Cancer Institute (Schagen et al., 1999; van Dam et al., 1998) published reports that included a control group of women with axillary-lymph node negative breast cancer who did not receive any adjuvant therapy.

They found that, at an average interval of two years post-treatment, there was a significantly higher frequency of cognitive decline, both as reported subjectively and as measured by standardized neuropsychological tests, in those breast cancer patients who received adjuvant chemotherapy relative to the control group. Their data suggest a relationship between chemotherapy dose and risk of cognitive decline.

Brezden and colleagues (2000) compared two groups of female breast cancer patients, one during and one after receiving adjuvant chemotherapy, with a group of healthy, cancer-free controls. Women undergoing chemotherapy scored significantly lower on indices of cognitive function than their control counterparts, even after controlling for age, education level, menopausal status, and mood disturbances.

Ahles and colleagues (2002) examined the cognitive functioning of long-term survivors of breast cancer who had received adjuvant chemotherapy and compared their scores to breast cancer survivors who had received local surgery only. After controlling for age and education, the chemotherapy-treated group, as a whole, performed significantly poorer on the battery of neuropsychological tests than their no-chemotherapy counterparts, with performance particularly marked in the domain of psychomotor functioning. A significant association between the number of cycles of chemotherapy received and neuropsychological observed deficits was also reported. Overall, these data, particularly the observed dosage effect supports a causal link between chemotherapy and cognitive dysfunction.

Using a cross-sectional design, Castellon et al. (2004) evaluated the cognitive functioning of breast cancer survivors who received adjuvant treatment (chemotherapy

and/or tamoxifen), no adjuvant treatment (surgery only), and a healthy, demographically matched, non-breast cancer comparison group. The adjuvant treatment arm was associated with significant cognitive decline in visual memory, visuospatial functioning, and verbal learning. Moreover, participants who received a combination of adjuvant treatments, chemotherapy and tamoxifen, fared significantly poorer on the above-mentioned cognitive domains, as compared to healthy controls. These group differences were not the result of demographic factors, self-reported mood, or fatigue, and suggests that it is necessary to differentiate the potential adverse effects of adjuvant tamoxifen from adjuvant chemotherapy.

Finally, Wefel, Lenzi, Theriault, Davis et al. (2004) conducted the only prospective study to be published in this area that included baseline cognitive testing prior to the start of adjuvant chemotherapy. This cohort consisted of 18 breast cancer survivors who also underwent testing at two additional time points - three weeks and one-year post-chemotherapy. At baseline, 33% of the breast cancer survivors showed cognitive impairment as defined by a score of either 1.5 standard deviations below the mean on two or more tests, or below 2.0 standard deviations on one test. This increased to 61% at short-term follow-up, and subsequently declined to 50% at long-term follow-up. The cognitive domains most negatively affected were attention, learning, and speed of information processing. These findings were consistent with the notion that a subgroup of breast cancer survivors is particularly susceptible to the adverse cognitive effects of adjuvant chemotherapy.

The seven studies described above were combined using a meta-analytic technique

to address the question as to the extent of cognitive decline associated with adjuvant chemotherapy as a treatment for breast cancer. Although meta-analyses often include a larger number of studies and have a wider scope, this meta-analysis is limited solely to breast cancer. We were concerned that differences in chemotherapy regimens among different cancer types may have obscured findings. Moreover, given the importance of this topic - the increasing number of options available to women with breast cancer and their associated cognitive side-effects - such a pointed evaluation of the literature is timely.

METHOD

Sampling Procedure

A computerized literature search of abstracts from Cancerlit, Medline, and PsychInfo was performed to locate pertinent articles published between 1966 to the present time. The following keywords, in different combinations, were used: breast cancer, chemotherapy, tamoxifen, neuropsychology, cognitive, cognition, memory, attention, executive function, and speed of processing. The reference lists of retrieved articles and review articles were also searched.

Inclusion and exclusion criteria

The literature search retrieved more than 200 abstracts. To be included in this meta-analysis, a study had to present original neuropsychological data written in English and includes female participants that have been diagnosed at any breast cancer stage, and received adjuvant chemotherapy. Given that we examined the neuropsychological impact

following adjuvant chemotherapy among breast cancer patients only, studies that included other types of cancer but did not isolate breast cancer data were excluded. Self-report data describing cognitive symptoms were also excluded.

The above requirements were rigorous to ensure the overall integrity of the meta-analytic findings. Finally, our inclusion/exclusion criteria also omitted the possible impact of tamoxifen, because in the few studies that did address this issue, the relevant data were not available to distinguish these sub-groups. The same applied to the menopausal status of participants.

Sample description

Ultimately, the following seven studies met our inclusion criteria for the meta-analysis: (i) Ahles et al. (2002; only breast cancer group used in analysis), (ii) Brezden et al. (2000), (iii) Castellon et al. (2004); (iv) Schagen et al. (1999), (v) van Dam et al. (1998), (vi) Wefel, Lenzi, Theriault, Davis et al. (2004), and (vii) Wieneke and Dienst (1995). With the exception of Wefel, Lenzi, Theriault, Davis et al. (2004), all others were retrospective in nature. All participants were screened for metastatic disease, neurologic and psychiatric problems, including drug and alcohol abuse. Neuropsychological assessment was conducted in either English (Ahles et al., 2002; Brezden et al., 2000; Wieneke & Dienst, 1995) or Dutch (Schagen et al., 1999; van Dam et al., 1998). The recruitment procedure was similar across all studies, namely via contacts with oncologists or through a cancer registry. The treatment group of breast cancer patients was classified as stage I to IV disease, with the majority having a Stage I or II original diagnosis. Adjuvant

chemotherapy regimens varied slightly between studies, although all were well-known. The most widely used combinations consisted of several cycles of: (i) cyclophosphamide, doxorubicin, fluorouracil, (ii) cyclophosphamide, epirubicin, fluorouracil, and (iii) CMF. Standard doses were administered in all studies, with the exception of van Dam and colleagues' (1998), who also included a high-dose chemotherapy group. These patients received a large dose of cyclophosphamide (six times the standard dose), in addition to thiopeta and carboplatin. The time since treatment varied considerably within and between studies. For example, some patients were assessed during treatment and others as much as five years post-treatment. Given the small number of studies, a differentiation of the results on this basis was not feasible. There were differences in the types of control groups employed across studies. Ahles, Schagen, and van Dam and their colleagues' (2002; 1999; 1998, respectively) recruited breast cancer volunteers matched for age who were treated with surgery and/or radiation therapy (excluding central nervous system radiation) but did not receive chemotherapy treatment. Note that the control group employed by Schagen and van Dam's group (1999; 1998) was identical, possibly impacting the independence of the studies. Brezden et al. (2000) obtained a group of healthy female volunteers to serve as a comparison group to their breast cancer participants. Wieneke and Dienst (1995) did not include a control group, relying on comparisons to normative samples only. As well as their treatment arm, Castellon et al. (2004) included two comparison groups - breast cancer survivors (no adjuvant treatment) and healthy control subjects. In the case of their study, we selected the former as the comparison group for our meta-analysis. Finally, Wefel,

Lenzi, Theriault, Davis et al. (2004) used a within-subject design, with the baseline condition serving as the control measure.

DATA ANALYSIS

Most of the studies employed standardized clinical neuropsychological measures, although a few experimental tests were also included. Because most investigators used multiple measures, tests were conceptually grouped according to the following cognitive domains: (i) simple attention, (ii) working memory, (iii) short-term memory, (iv) long-term memory, (v) speed of information processing, (vi) language, (vii) spatial, and (viii) motor abilities. Reported statistics from Schagen et al. (1999) were adjusted for IQ, while those of Wieneke and Dienst (1995) were corrected for age, education, and gender. Wefel, Lenzi, Theriault, Davis et al. (2004) data was based on published norms. Although the values associated with the remaining studies' were unadjusted, control participants were matched for age and education, thus reducing potential biases.

In this study, weighted Hedge's d effect sizes were calculated using Schwarzer's (1988) meta-analytic software and the underlying assumption of homogeneity of effect size was considered. This method transforms reported statistics into effect sizes using treatment-control comparisons. Studies by Ahles and Schagen and colleagues' (2002, 1999, respectively) each had one treatment and one control group, allowing for straightforward dichotomous comparisons for each neuropsychological test in a given cognitive domain. The studies by Brezden and van Dam, and colleagues' (2000 and 1999, respectively) on the other hand, each employed two treatment groups and one control group, thus yielding two

dichotomous comparisons per measure. To control the number of effect sizes' generated, a weighted average (based on the sample size of the treatment-control comparisons) was calculated such that each study, regardless of the number of treatment-control comparisons and neuropsychological measures, contributed a single effect size per cognitive domain. The study by Wieneke and Dienst (1995) contained only one group of participants, equivalent to a treatment group, and made comparisons to published norms. In order to use Schwarzer's method, a sample size from a comparison group was required. Given the small number of studies available, we elected to include this one, and simulate a control group sample size of $n = 1$. This represents the most conservative estimate of a comparison group and is therefore the least likely to overestimate the index of any cognitive decline generated by the meta-analysis. In the case of Wefel, Lenzi, Theriault, Davis et al. (2004), given the prospective design of the study, the baseline performance of subjects was compared to their post-chemotherapy scores (short - and long-term time points).

Table 7 lists the tests included in the meta-analysis and the number of effect sizes generated for each cognitive domain.

RESULTS

To ensure that the results were not skewed by van Dam et al.'s (1998) high dose treatment group, effect sizes were generated with and without the data associated with this group. However, no significant differences were found among any of the eight cognitive domains, whether the high dose treatment group was included or not. Given that the high

Table 7. List of measures associated with individual cognitive domains and number of effect sizes.

Cognitive domain	Measures included in meta-analysis ^a	No. of effect sizes generated ^b
Simple attention	Trails A ^{1,3,4,5,6,7,8,9} ; Vigilance task (# correct) ¹ ; Vigilance task (reaction time) ¹ ; Digit Span (F) ^{3,4,5,6}	14
Working memory	Trails B ^{3,4,5,8} ; Digit Span (B) ^{3,4,5,8} ; Stroop test ^{3,4,5,7,8} ; PASAT ⁷ ; Arithmetic ⁸	15
Short-term memory	Logical Memory I ^{1,7} ; Visual Reproduction I ¹ ; CVLT 1-5 total ^{1,6,7} ; CVLT List B ⁷ ; CVLT short delay ^{1,6,7} ; Rey 15 words Recall ^{3,4,5} ; Complex Figure Recall ^{3,4,5} ; WMS Immediate Recall (visual) ^{3,7}	18
Long-term memory	Logical Memory II ^{1,7} ; Visual Reproduction II ¹ ; CVLT Long Delay ^{1,6,7} ; CVLT Long Delay (recog.) ¹ ; Rey 15 Words Delayed Recall ^{3,4,5} ; Rey 15 Words Delayed Recognition ^{3,4,5} ; Complex Figure Delayed Recall ^{4,5,6,7} ; WMS Delayed Recall (visual) ^{3,7} ; Verbal & Nonverbal Selective Reminding Test (LTS & Delayed) ⁸	21
Speed of processing	Digit Symbol ^{1,3,4,5,8} ; Test D2 (GZ-F) ^{3,4,5} ; Fepsy Visual Reaction (D, ND) ^{3,4,5} ; Fepsy Binary Choice ^{3,4,5} ; Fepsy Visual Search ^{3,4,5} ; CalCAP Median SRT, CRT, & Accuracy ⁷	23
Language	Vocabulary subtest ¹ ; Reading subtest (WRAT-R) ¹ ; Boston Naming Test ¹ ; Word Fluency ^{1,3,4,5,7,8} ; Animal Fluency ⁷ ; 2 Language subtests of the High Sensitivity Cognitive Screen ²	12
Spatial abilities	Block Design ^{1,6,7,8,9} ; Complex Figure (Copy) ^{3,4,5,6,7}	10
Motor abilities	# Sequences (RT, LT) ¹ ; Avg Finger-tapping (D, ND) ¹ ; Fepsy Finger-tapping (D, ND) ^{3,4,5} ; Grooved Pegboard (D, ND) ^{6,8,9}	16

a. Column lists the neuropsychological tests and authors, where 1 = Ahles et al.

(2002); 2 = Brezden et al. (2000); 3 = Schagen et al. (1999); 4 = van dam et al. (1998; standard dose); 5 = van dam et al. (1998; high dose), 6 = Wieneke & Dienst (1995), 7 = Castellon et al. (2004), 8 = Wefel et al. (2004; short-term), 9 = Wefel et al. (2004; long-term).

b. Refers to the total number of effect sizes generated across studies. For example, in the domain “simple attention”, the 14 effect sizes comprise 8 from Trails A, 2 from a vigilance task, and 4 from digit span (see superscripts attached to each test). Note that some tests have multiple components (example D & ND would generate two effect sizes).

LTS = long-term storage. D = dominant, ND = non-dominant. RT = right; LT = left.

dose and standard dose groups were separate experimental conditions, both were included in the analysis.

Table 8 shows the weighted effect sizes according to cognitive domain. Also included are the number of studies contributing to each effect size, the weighted pooled effect size, number of subjects associated with each effect size, 95% confidence intervals, and fail-safe N values for each cognitive domain. *Hedges' d* values ranged from -0.13 to -0.37, with the modal value falling at -.24, interpreted as a small to medium effect size. The negative effect sizes reflect poorer cognitive functioning as compared to control participants (baseline data in the case of Wefel, Lenzi, Theriault, Davis et al., (2004)) despite being matched for age and education. With the exception of simple attention, all other domains of neuropsychological functioning gave rise to statistically significant differences ($p \leq .05$ to .0001), indicating lower test scores for the groups of chemotherapy patients than for the groups with which they were compared. The average overall effect

Table 8. Weighted pooled effect sizes and tests of heterogeneity for each cognitive domain.

Cognitive domain ^a	# of studies ^b	Weighted pooled effect size (d) ^c	n ^d	95% CI ^e	Fail-safe N ^f
Simple attention ^{1,3,4,5,6,7,8,9}	8	-.13	366	.32/+0.07	10
Working memory ^{3,4,5,7,8}	5 (3)	-.24*	266	-.47/-0.01	7
Short-term memory ^{1,3,4,5,6,7}	6	-.31**	328	-.53/-0.09	9
Long-term memory ^{1,3,4,5,6,7,8}	7 (1)	-.26*	364	-.46/-0.05	10
Speed of processing ^{1,3,4,5,7,8}	6 (2)	-.22*	336	-.43/+0.00	8
Language ^{1,2,3,4,5,7,8}	7 (2)	-.37***	372	-.56/-0.18	12
Spatial abilities ^{1,3,4,5,6,7,8,9}	8	-.30**	344	-.49/-0.10	11
Motor abilities ^{1,3,4,5,6,8,9}	7	-.24*	325	-.52/-0.04	8
Overall		-.26	338		

^a Column lists the cognitive domains and relevant studies included, where 1 = Ahles et al.

(2002); 2 = Brezden et al. (2000); 3 = Schagen et al. (1999); 4 = van dam et al. (1998; standard dose); 5 = van dam et al. (1998; high dose), 6 = Wieneke & Dienst (1995), 7 = Castellon et al. (2004), 8 = Wefel et al. (2004; short-term), 9 = Wefel et al. (2004; long-term).

^b Column lists the number of studies included per cognitive domain. Some studies were removed to achieve homogeneity (number in parentheses); these were - working memory, see studies 1,6,9; long-term memory, see 9; speed of processing, see 6,9; language, see 6,9.

^c Hedge's d weighted pooled effect size.

^d Total number of subjects (experimental and control) per effect size.

^e Confidence interval.

^f Column lists the number of studies that would be required to change the results from significant to non-significant based on a d of .35, mid-way between a small to medium effect size.

* $p < .05$; ** $p < .005$; *** $p < .0001$

size, indicating an overall neuropsychological deficit index of $d = -.26$, falls in the small to medium range. The largest differences ($\pm CI_{.95}$) were obtained in language ($d = -.37$) and short-term memory ($d = -.31$), which approaches a moderate effect. Similar to other statistical procedures, meta-analytic techniques must also meet underlying assumptions to ensure unbiased conclusions. One of the most commonly assessed assumptions is the test of homogeneity of effect sizes that if rejected (referred to as heterogeneity) suggests that the studies included in the meta-analysis contain systematic variation, possibly better accounted for by a moderator variable (i.e., gender, education, socio-economic status). Heterogeneity can be corrected by successively eliminating outliers until homogeneity is achieved. For the present meta-analysis, the homogeneity of cognitive domains was tested using chi-square and was significant among four cognitive domains - working memory, long-term memory, speed of information processing, and language. In these cases, the data associated with the cognitive domains giving rise to outliers were removed and homogeneity was achieved. Table 8 lists the studies that contributed to the heterogeneity. Hypotheses underlying this heterogeneity are discussed in the next section.

The fail-safe N refers to the number of non-significant, unpublished, or missing studies that would be required to change the meta-analytic results from significant to non-significant. As a conservative guideline, Rosenthal (1991) has proposed a critical value such that the true effect differs from zero when the fail-safe number exceeds five times the number of studies included in the meta-analysis plus 10 ($5k+10$). Using Orwin's (1983)

formula (see Lipsey & Wilson, 2001), our fail-safe number of 7 to 12 studies across domains (see Table 8) falls short of Rosenthal's (1991) critical cutoff of 45.

DISCUSSION

Present findings & implications

Pooling the results from seven studies and considering more than 300 subjects, this meta-analysis indicates that, overall, adjuvant chemotherapy treatment for breast cancer patients results in a small but significant decline in global cognitive functioning. The cognitive domains most negatively affected were language, short-term memory, and spatial abilities, with differences in mean scores ranging from about one-quarter to one-half a standard deviation. Statistically significant, albeit lower deterioration, was also found in the domains of working-, and long-term memory, speed of processing, spatial and motor abilities - findings also consistent with previous reports suggesting that the effects of adjuvant chemotherapy on cognitive functioning were global in nature.

None of the individual studies that contributed to the current meta-analysis found any association between cognitive performance and age, education, affective well-being, fatigue or menopausal status (Ahles et al., 2002; Brezden et al., 2000; Castellon et al., 2004; Schagen et al., 1999; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis et al., 2004; Wieneke & Dienst, 1995); a minority of studies found a relationship between self-reported cognitive complaints and/or fatigue and psychological distress (Castellon et al., 2004; van Dam et al., 1998).

To our knowledge this is the first paper to offer a quantitative analysis of the

neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer. It is important to note that although these findings do offer evidence for cognitive decline among breast cancer patients, none of the findings reached clinically significant impairment levels. However, test scores alone do not capture the complete picture of a patient's functioning (Hannay & Lezak, 2004). In the first-ever prospective study in this area (Wefel et al. 2004), self-reported difficulties to complete work-related duties apparently improved as neuropsychological test scores ameliorated.

Other literature

Anderson-Hanley et al. (2002, 2003) conducted a meta-analysis of the cognitive effects associated with various cancer types and adjuvant treatments, reporting a one- to two-thirds standard deviation decline in cognitive functioning. While our meta-analysis was exclusively based on studies that evaluated cognitive deficits in breast cancer patients, our findings are in line with Anderson-Hanley et al.'s (2002, 2003) data.

Several qualitative reviews describing cognitive dysfunction following adjuvant therapy have appeared in the literature in recent years (Ahles & Saykin, 2002; Barton & Loprinzi, 2002; Bender et al., 2001; Freeman & Broshek, 2002; Olin, 2001; O'Shaughnessy, 2003a; O'Shaughnessy, 2003b; Rugo & Ahles, 2003; Schagen, Muller, Boogerd, & van Dam, 2002; Silberfarb, 1983). Most narratives identify deterioration in concentration, memory, speed of information processing, and motor abilities. Our findings confirm these cognitive deficits and extend them to comprise language difficulties. Moreover, this meta-analysis quantified these cognitive deficits in the order of a loss of

one-quarter to one-half a standard deviation. Although acknowledging a small or subtle change, Rugo and Ahles (2003) propose that there may be sufficient evidence to raise informed consent issues.

In her review, Olin (2001) concluded that one in three breast cancer survivors are likely to experience cognitive deficits owing to adjuvant chemotherapeutic treatments. Similarly, O'Shaughnessy (2002) estimated that 15 to 25% of breast cancer patients treated with chemotherapy experience cognitive problems after treatment in comparison to only 10% of breast cancer patients who do not receive adjuvant chemotherapy. The current results do not contradict the hypothesis that such a subgroup exists, an idea that is being followed up by Ahles and colleagues (2002).

Potential impact of measurement problems on effect sizes

Collectively, all studies were retrospective and cross-sectional in design, with one exception (Wefel, Lenzi, Theriault, Davis et al., 2004). Our meta-analysis did not evaluate the influence of potential moderator variables such as age, education, time since completion of adjuvant chemotherapy and neuropsychological assessment, menopausal status (pre-versus post-menopausal), level of fatigue, mood disturbance (depression and/or anxiety), and inclusion of participants with other psychiatric/neurological conditions (e.g., alcohol/drug abuse); the division of the relatively small data sets into appropriate subgroups was not feasible.

Some studies reported a decline in performance on cognitive domains, while others did not, contributing to an overall heterogeneous profile in some domains. For example,

Castellon et al. (2004) did not find an effect of speed of information processing while Ahles et al. (2002) and van Dam et al. (1998) did. Our strategy to achieve homogeneity was to successively remove studies.

Of the three studies (Ahles et al., 2002; Castellon et al., 2004; Schagen et al., 1999) that evaluated the effects of adjuvant tamoxifen, only one (Castellon et al, 2004) found greater cognitive decline when chemotherapy was combined with tamoxifen than when used alone. Preliminary results do suggest that tamoxifen adversely impacts cognition, particularly in the form of memory problems (Paganini-Hill & Clark, 2000). Given that this anti-estrogen compound is prescribed in the majority of breast cancer cases, its use alone or in conjunction with chemotherapy with respect to cognitive functioning warrants further investigation.

Limitations of meta-analytic procedures

Historically, meta-analyses were conducted by those well versed in the language of statistical procedures; however, the greater availability of user-friendly software has enabled such techniques to be exploited more widely, making it all the more crucial to bear in the mind the limitations of such techniques as applied in the current application.

The fail-safe N (7 to 12 studies) provides an estimate of the number of unpublished null results that would be required to reduce the effect size to 0, and in this case, fell short of the critical cutoff of 45 (Rosenthal, 1991). Note that Rosenthal concedes that this estimate represents a conservative value (1991, p. 509) and that the fail-safe N formula is biased towards the inclusion of both a large number of studies and large effect sizes. At

the outset, the prospect of the present meta-analysis surpassing the critical cutoff was unlikely because it comprised a small number of studies and was further compounded by our hypothesis to expose subtle cognitive deficits. Indeed, the magnitude of our effect sizes is compatible with studies investigating related research domains of interest.

Meta-analytic techniques have been criticized for comparing apples to oranges and for including studies that are of poor quality, ultimately lending to a “garbage in – garbage out” phenomenon (Rosenthal & DiMatteo, 2001). We addressed these issues in two ways. First, we limited our focus to a specific cancer type in an effort to maintain homogeneity of standard chemotherapy regimens. Second, in contrast to many meta-analyses in the cancer literature (e.g., multi-site clinical trials), this one comprised far fewer studies, making the inclusion criteria all the more critical. We were admittedly conservative in this regard but made every attempt to not omit already scarce data. Efforts were made to acquire sufficient data to calculate effect sizes (e.g., contacting author; acquiring full dissertation) and where not feasible, excluded.

Four of the seven studies comprised more than one appropriate experimental group and if possible, we elected to treat them as separate treatment-control comparisons. Although the lack of independence is a concern, effect sizes were weighted according to sample size. Note that the two studies conducted by the Netherlands group of investigators (Schagen et al., 1999; van Dam et al., 1998) shared the same control group. Rosenthal and DiMatteo (2001) recommend that in such cases, more prudent strategies such as conservative averaging, for example, be employed. To address this point in our data, we compared the effect sizes associated with each domain that were generated using the data

from the Netherlands group. In each case except for one (spatial abilities), their values fell mid-way between the effects sizes obtained in the other groups. If the contribution of their effect sizes to the data set had been influencing the individual cognitive domains towards one extreme or the other, it would have been appropriate to weight the respective effect sizes. However, given our patterns, we felt that this was unnecessary.

Another caveat arising from the work by the Netherlands group concerns our inclusion of van Dam's and colleagues (1998) high dose treatment arm. Although their high dose data yielded effect sizes that appeared generally higher than those associated with their standard dose, we found no significant difference in the average effect size across domains when we compared these with and without van Dam's high dose data. For this reason, we opted to report the analysis that included the high dose data. We acknowledge that by doing so, we are inflating the individual domain effect sizes but with minimal statistical consequence. On the other hand, the inclusion of high dose data has important clinical relevance, given that women are being offered more aggressive adjuvant treatment. In spite of these concerns with regard to the data by Schagen and colleagues (1999) and van Dam and colleagues (1998), these studies were among the most comprehensive with respect to standardized neuropsychological measures.

Conclusion

Meta-analysis is an important statistical tool for combining data, particularly among clinical samples that are both time-consuming and costly to evaluate. The results presented here tentatively show that breast cancer survivors exposed to standard adjuvant

chemotherapy treatment may suffer subtle cognitive morbidity, as indexed by small to moderate effect sizes. These findings will contribute to the development of adjuvant chemotherapy protocols that minimize long-term cognitive decline.

STUDY 2

A shorter version of this manuscript was submitted to the Journal of Psycho-

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**The Cognitive Effects of Adjuvant Chemotherapy in Early Stage Breast Cancer:
A Prospective Study**

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ABSTRACT

Purpose: The primary purpose of this study was to evaluate the cognitive effects of adjuvant chemotherapy in post-menopausal breast cancer patients.

Patients and Methods: Breast cancer patients scheduled to receive adjuvant chemotherapy (n = 61) completed comprehensive cognitive testing before and after treatment. A control group of women receiving adjuvant hormonal therapy (n = 51), as well as a sample of healthy women (n = 28), were tested at comparable intervals.

Results: In two-group analyses, more of the chemotherapy patients than the hormonal patients showed reliable cognitive decline (26% and 8%, respectively, Relative Risk = 3.3).

Both patient groups showed a greater risk of reliable cognitive decline than healthy controls but, in these three-group analyses, the difference in risk between the chemotherapy and hormonal groups was no longer significant. Chemotherapy subjects showing decline were less educated and more likely to be on antidepressant medication at baseline than their counterparts who did not decline. Working memory was the cognitive domain most vulnerable to the effects of chemotherapy.

Conclusion: These data support previous findings of a subtle negative influence of chemotherapy on cognitive function in a subgroup of breast cancer patients. However, other factors associated with having a diagnosis of cancer also affect cognition. The results include a discussion of the importance of study design.

INTRODUCTION

With increasing numbers of breast cancer patients achieving complete physical recovery and looking to resume normal lives, there is a growing concern about the long-term side effects of treatments. Many cancer patients complain of “chemo fog” or “chemo brain”, cognitive changes that they attribute to their chemotherapy. These changes seem to be quite persistent in some cases, and so may have important implications for quality of life.

Several studies of chemo fog have now been conducted in breast cancer patients (Ahles et al., 1996; Ahles et al., 2002; Brezden et al., 2000; Castellon et al., 2004; Donovan et al., 2005; Fan et al., 2005; Hurria et al., 2006; Jenkins et al., 2006; Schagen et al., 1999; Schagen et al., 2002; Scherwath et al., 2006; Servaes, Verhagen, & Bleijenberg, 2002; Shilling et al., 2005; Tchen et al., 2003; van Dam et al., 1998; Wefel, Lenzi, Theriault, Davis et al., 2004; Wieneke & Dienst, 1995), with most of them finding reduced cognitive function in those treated with chemotherapy. Rates of cognitive impairment as high as 75% have been reported (Wieneke & Dienst, 1995). In most cases, findings indicate subtle effects on memory and mental processing speed.

Most of these studies have been cross-sectional and retrospective. This makes interpretation difficult, as it has been shown that there is an increased risk of cognitive impairment in cancer patients who have had *no* chemotherapy exposure (Meyers et al., 1995; Wefel, Lenzi, Theriault, & Buzdar et al., 2004). Thus, assessment before and after chemotherapy is necessary in order to conclude that any cognitive deficits observed following chemotherapy are attributable to chemotherapy exposure. The few prospective studies that have been conducted (Bender et al., 2006; Jenkins et al., 2006; Shilling et al., 2005; Wefel, Lenzi, Theriault, & Davis et al., 2004), while reporting smaller effect sizes

than cross-sectional studies, have generally found an increased risk of cognitive decline in chemotherapy patients (Bender et al., 2006; Shilling et al., 2005; Wefel, Lenzi, Theriault, & Davis et al., 2004). However, most of these studies failed to include a non-chemotherapy control group of breast cancer patients, and thus did not account for other disease- and treatment-related factors that might have given rise to performance decrements. The only prospective study to include a breast cancer control group found no group differences in either mean post-treatment cognitive function or rate of reliable cognitive decline (Jenkins et al., 2006). Thus, the literature remains far from conclusive.

This paper describes the results of a prospective study evaluating the cognitive effects of adjuvant chemotherapy in breast cancer patients. Patients receiving adjuvant hormonal therapy without chemotherapy were selected as our principal control group, to account for other disease and treatment factors that might contribute to cognitive change in cancer patients. Given recent findings that hormonal therapies may also affect cognition (Bender et al., 2006; Eberling et al., 2004; Paganini-Hill & Clark, 2000; Jenkins et al., 2004; Shilling et al., 2003), we added a small group of healthy control subjects. We expected that the chemotherapy-treated patients would be more likely to show cognitive decline than either the patients receiving hormonal therapy only or the healthy controls.

METHOD

Participants

Two groups of early stage breast cancer patients were recruited from the Ottawa Hospital Cancer Centre in Canada. One group received standard dose adjuvant chemotherapy with or without hormonal treatment (chemotherapy group), the other received adjuvant hormonal therapy only (hormonal group). We included only post-

menopausal women between 50 and 65 in order to reduce variability in cognitive function associated with age (Howieson, Loring, & Hannay, 2004) and circulating estrogen levels (Eberling et al., 2004). Patients were excluded if they had a previous history of cancer, chemotherapy, or radiation; advanced disease (metastasis beyond axillary lymph nodes); neo-adjuvant therapy; or unstable psychiatric, neurological, or substance use disorders that might affect cognition. A convenience sample of healthy postmenopausal women in the same age range was recruited through local advertising. The study was approved by the ethics board of the Ottawa Hospital and written informed consent was obtained from all participants. Table 9 lists relevant demographic and clinical characteristics of the groups.

Meta-analyses of cognitive function in breast cancer patients (Stewart et al., 2006; Falsetti et al., 2005) indicate a small to medium effect size in most cognitive domains. Accordingly, we set our target sample size at 60 subjects for each of the treatment groups in order to yield 80% power to detect a medium effect size (Cohen, 1988).

Assessment

A baseline assessment including clinical history, neuropsychological testing, and a mood rating scale was conducted after surgery in the patient groups and prior to initiation of any chemotherapy. Participants were reassessed four to five months later in most cases (following the last chemotherapy cycle in the chemotherapy group).

The neuropsychological tests, organized according to the cognitive domain they represent, are described in Table 10. A total of 23 scores from 18 neuropsychological tests were analyzed. The Quick Test (Ammons & Ammons, 1962), a measure of receptive vocabulary, was used to estimate IQ. Psychological distress was assessed using three

Table 9. Demographic and clinical characteristics of chemotherapy and hormonal groups.

Characteristic	Chemotherapy (N=61)	Hormonal (N=51)	p levels of significant findings
Age (in years at baseline)			
Mean (SD)	57.5 (3.7)	57.9 (4.4)	
Min/Max	50-66	50-65	
Education (in years at baseline)			
Mean (SD)	14.5 (3.2)	14.3 (3.3)	
Min/Max	8-23	9-23	
Estimated verbal IQ (at baseline)			
Mean (SD)	107.6 (10.1)	106.8 (10.5)	
Min/Max	87-130	84-135	
Proportion on depression meds (at baseline)	11.5% (n=7)	13.7% (n=7)	
Test-retest interval (in days)			
Mean (SD)	147.3 (35.8)	158.1 (31.2)	
Min/Max	91-252	119-245	
Stage of disease			p <.0001
0	0	0	
I	29.5% (n=18)	87.8% (n=43)	
II	65.6% (n=40)	12.2% (n=6)	
III	4.9% (n=3)	0	
Type of chemotherapy		N/A	
FEC 100	51% (n=31)		
AC/AC-Taxol	27.9% (n=17)		
CEF	8.2% (n=5)		
FAC	6.6% (n=4)		
Other	6.5% (n=4)		
No. chemotherapy cycles		N/A	
Mean (SD)	5.6 (1.2)		
Min/Max	4-10		
Mean interval between last chemotherapy cycle	30.9 (26.2)	N/A	

 and retest (SD)

Type of hormonal therapy prescribed			p < .0001
Tamoxifen	36.1% (n=22)	60.8% (n=31)	
Arimidex	21.3% (n=13)	29.4% (n=15)	
Other	11.5% (n=7)	9.8% (n=5)	
None	31.1% (n=19)	0	
Proportion starting hormonal therapy prior to second testing	20% (n=12)	100% (n=53)	p < .0001
Proportion exposed to radiation prior to second testing	4.9% (n=3)	75% (n=38)	p < .0001

Notes: SD= standard deviation; IQ= intelligence quotient as measured by the Quick Test

(Ammons & Ammons, 1962); N/A=not applicable.

Table 10. Test battery identified by cognitive domain.

Tests (by Cognitive Domain)	Description	Measure of interest	Measure abbreviation
<u>Executive function</u>			
Paced Auditory Serial Addition Task (Gronwall, 1977)	Addition of 60 pairs of randomized digits such that each digit is added to the preceding one; Digits presented auditory modality at 1.2, 1.6, 2.0, and 2.4 sec on 4 consecutive trials	2.4 sec, total correct	PASAT 2.4s, total correct
Trail Making Test Part B (Army Individual Test Battery, 1944)	Alternately connect numbers and letters randomly distributed on a page	Part B, completion time	Trails B
Wisconsin Card Sorting Test (Heaton, 1981)	Sort cards in relation to key cards using different strategies deduced from examiner feedback; maximum of 128 cards	Total number of trials administered	WCST Trials administered
<u>Language function</u>			
Boston Naming Test (Goodglass et al., 1983)	Naming of 60 drawn objects	Total raw score	Boston Naming Test total
Controlled Oral Word Association Test (Benton, 1994)	Generation of words beginning with letters F, A, & S; 60 sec time limit per letter	Total of letters F, A, & S	FAS, total correct
<u>Motor</u>			
Grooved Pegboard (Reitan & Wolfson, 1985)	Insertion of 25 pegs in slotted holes with each of the dominant and non-dominant hand	Total completion time, dominant plus non-dominant hands	Grooved Pegboard, D & ND
<u>Processing speed</u>			
Digit-Symbol Coding from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997b)	Copying symbols to correspond with numbers according to a key	Total raw score	Digit-Symbol Coding
Symbol Search from the WAIS-III	Visual scanning and matching of nonsense symbols	Total raw score	Symbol Search
Trail Making Test Part A	Connect 25 numbers in numerical sequence	Part A, completion time	Trails A

<u>Verbal learning and memory</u>			
California Verbal Learning Test II (CVLT-II; Delis et al., 2000), List A Trial 1	Immediate recall of a word list following first presentation		CVLT, List A Trial 1
CVLT-II, Long-Delay Free Recall	Delayed recall of the list words		CVLT, Long-Delay Free
CVLT-II, Long-Delay Recognition	True positives plus true negatives on delayed recognition		CVLT, Long-Delay Recog
Logical Memory II from the Wechsler Memory Scale-III (WMS-III; 1997b)	Recall of two stories following a 25-to-35- minute delay	Delayed recall, total score	Logical Memory II
<u>Visual learning and memory</u>			
Rey Visual Learning Test (RVLT; Rey, 1968) Free Recall Trial 1	Immediate recall of 15 nonsense designs following first presentation	Trial 1, total score	RVLT, Trial 1
RVLT Long Delay Free Recall Total	Delayed recall of the 15 nonsense designs	Total score	RVLT, Long-Delay Free
RVLT Long Delay Recognition	Delayed recognition of the 15 nonsense designs	Total score	RVLT, Long-Delay Recog
Family Pictures II from the WMS-III	Delayed recall of thematic pictures	Delayed recall, total score	Family Pictures II
<u>Visuospatial function</u>			
Block Design from the WAIS-III	Construction of geometric designs using blocks	Total raw score	Block Design
<u>Working memory</u>			
Arithmetic from the WAIS-III	Mental arithmetic problem-solving	Total raw score	Arithmetic
Consonant Trigrams (Brown, 1958)	Retain 3 consonants while performing serial subtraction for 0,3, 9, or 18 sec	Total score	CCC Total
Digit Span from the WAIS-III	Forward and backward recitation of a string of numbers	Digits forward plus digits backwards	Digit Span (F & B)
Letter-Number-Sequencing from	Mental re-ordering of alphanumeric sequences	Total raw score	Letter-Number-

the WAIS-III Spatial Span from the WMS-III	Forward and backward repetition of visuospatial sequences	Total raw score	Sequencing Spatial Span
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subscale scores from the Profile of Mood States (POMS; McNair et al., 1992)-Depression-Dejection, Fatigue-Inertia, and Tension-Anxiety.

Data Analysis

The Statistical Package for the Social Sciences (version 13.0) was used for all data analyses. The alpha level was set at .05. Note that no Bonferroni correction was applied.

Selection of Covariates

Age, education, and IQ, as well as the three POMS scores, were considered for inclusion as covariates using a two-pronged approach as depicted in Figure 1. When using age, education, or IQ as covariates, their raw baseline values were used. The state-dependent POMS measures were covaried by regressing these variables on the respective neuropsychological measures at Time 1 (T1) and Time 2 (T2; Figure I), and then using the residuals from these regressions rather than the raw neuropsychological test scores as the dependent variables. Table 11 shows which covariates were used with each of the neuropsychological measures.

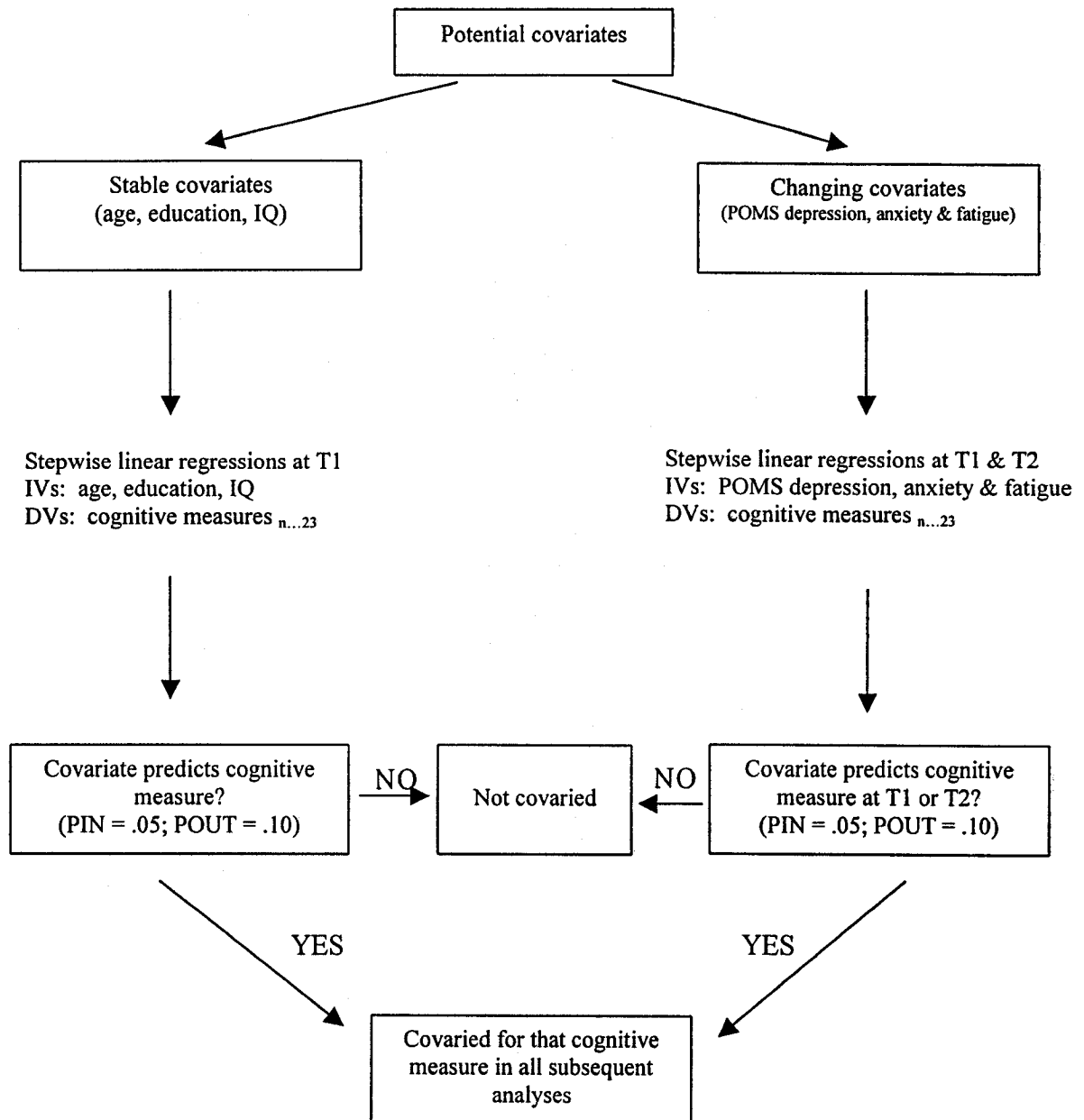


Figure 1. Flowchart describing process for selection of covariates.

Note. Treatment groups were collapsed for these analyses. DV = dependent variable; IV = independent variable; T1 = Time 1; T2 = Time 2

Table 11. Covariates used with the various neuropsychological measures.

	Stable covariates			Changing covariates		
	Age	Education	IQ	Tension-Anxiety	Depression-Dejection	Fatigue-Inertia
<u>Cognitive domain/Measure</u>						
<u>Executive function</u>						
PASAT, 2.4s, total correct		✓			✓	✓
Trails B		✓			✓	
WCST, Trials administered		✓				
<u>Language</u>						
Boston Naming Test, total	✓		✓	✓	✓	✓
FAS, total correct			✓			✓
<u>Motor</u>						
Grooved Pegboard, D & ND		✓				
<u>Processing Speed</u>						
Digit-Symbol Coding		✓				
Symbol Search	✓	✓				
Trails A						
<u>Verbal Learning and Memory</u>						
CVLT, List A Trial 1	✓					
CVLT, Long-Delay Free			✓			
CVLT, Long-Delay Recog			✓	✓	✓	
Logical Memory II		✓				
<u>Visual Learning and Memory</u>						
RVLT, Trial 1*						
RVLT, Long-Delay Free		✓				
RVLT, Long-Delay Recog			✓			
Family Pictures II*						

<u>Visuospatial</u>			
<u>Function</u>			
Block Design	✓	✓	✓
<u>Working Memory</u>			
Arithmetic	✓	✓	✓
CCC Total	✓		
Digit Span	✓		
(F & B)			
Letter-Number-		✓	✓
Sequencing			
Spatial Span	✓		

Group Comparisons on Cognitive and Mood Measures

Mixed design ANOVA was used to examine group differences in cognitive and mood measures at T1 and T2. Where age, education, or IQ was included, ANCOVA was used.

Individual Change Analyses

Given that group comparisons can obscure clinically significant cognitive decline in individual cases, our data were subjected to additional analyses based on a standardized-regression based (SRB) approach to cognitive change (McSweeney et al., 1993; Sawrie et al., 1999). This method uses the test/retest scores of a reference group (the hormonal group in this case) to develop a regression equation that predicts retest scores. The difference between the predicted and obtained scores divided by the standard error of the estimate produces a standardized change score that reflects the direction and magnitude of change, controls for test-retest confounds (e.g., practice effects, regression-to-the-mean), and simultaneously allows for comparisons across measures. While other methods of individual change over time have been employed (e.g., variations of the reliable change

index) in this research domain (e.g., Shilling et al., 2005), they cannot accommodate for the inclusion of moderator variables, regression-to-the-mean, and comparisons across measures. For these reasons, we selected the SRB approach to the analysis of our data.

Reliable cognitive decline was defined as an SRB change score greater than or equal to 2 standard deviations below the reference group on 2 or more of the 23 cognitive measures. Reliable cognitive improvement was defined as a change score greater than or equal to two standard deviations above the mean on two or more cognitive measures. Chi-square was used to determine group differences in frequency of reliable cognitive decline and improvement.

Cognitive Domain Summary Scores

Cognitive composite scores were computed by adding the SRB change scores for all variables within a given cognitive domain (Table 10), and were compared for chemotherapy and hormonal groups using t-tests.

RESULTS

Rate of attrition was identical (7.5%) in both treatment groups. Three of the chemotherapy subjects were excluded due to cancer recurrence. In all remaining cases, attrition was due to subjects declining retest. Only data from patients who completed both testing sessions were analyzed. The two patient groups did not differ from each other with respect to age, education, IQ, or test-retest interval (Table 9). There were more patients with stage II and III disease in the chemotherapy group than in the hormonal group.

Group Comparisons on Cognitive and Mood Measures

Table 12 presents the means and standard deviations of the patient groups on the 23 cognitive measures, as well as the results of the ANOVAS and ANCOVAS pertaining to these measures. The single main effect of group favoured the chemotherapy subjects. The two main effects of time both indicated better performance at T2 than at T1. There were four group-by-time interactions. These involved measures of memory and working memory and indicated less improvement in the chemotherapy group than in the hormonal group.

The means and standard deviations of the POMS measures, as well as the results of ANOVAs involving these variables, appear in Table 13. There were no main effects of group. Scores on Tension-Anxiety decreased, and scores on Fatigue-Inertia increased, from T1 to T2. Interactions were noted for Depression-Dejection and Tension-Anxiety, with the chemotherapy group showing larger decreases than the hormonal group. There was a trend toward a greater increase in fatigue in Fatigue-Inertia in the chemotherapy group.

Individual Change Analyses

Twenty-six percent (16 of 61) of the chemotherapy subjects showed reliable cognitive decline as compared to 8% (3 of 51) of the hormonal group ($RR = 3.3$, $\chi^2 = 6.4$, $p = .01$). There was no difference in the frequency of reliable cognitive improvement (3% in chemotherapy group, 6% in hormonal group; $p = .51$).

Within the chemotherapy group, there were no differences between those who declined and those who did not in terms of chemotherapy regimen, number of cycles, age,

Table 12. Unadjusted means and standard deviation for chemotherapy and hormonal groups on cognitive measures, and results of ANOVAs and ANCOVAs on these measures.

Cognitive domain/ Measure	Time 1				Time 2				Significance
	Chemo Mean (SD)	n	Hormonal Mean (SD)	n	Chemo Mean (SD)	n	Hormonal Mean (SD)	n	
<u>Executive function</u>									
PASAT, 2.4s, total correct	40.4 (9.1)	52	39.6 (9.7)	42	43.7 (10.1)	47	41.9 (9.3)	40	G: ns T: ns GxT: ns
Trails B	73.1 (29.6)	61	70.1 (22.0)	51	69.5 (27.8)	61	70.3 (22.0)	51	G: ns T: ns GxT: ns
WCST, Trials administered	100.7 (21.9)	59	104.1 (23.9)	50	96.8 (22.3)	59	100.8 (23.6)	48	G: ns T: ns GxT: ns
<u>Language</u>									
Boston Naming Test, total	54.8 (4.9)	58	54.1 (5.4)	51	55.6 (4.8)	58	55.1 (4.9)	51	G: ns T: ns GxT: ns
FAS, total correct	40.7 (12.7)	60	37.7 (11.0)	51	39.5 (12.4)	60	39.0 (10.9)	51	G: ns T: ns GxT: ns
<u>Motor</u>									
Grooved Pegboard, D & ND	154.5 (40.9)	60	159.1 (29.9)	49	151.9 (33.8)	60	153.6 (25.1)	48	G: ns T: ns GxT: ns
<u>Processing Speed</u>									
Digit-Symbol Coding	67.0 (12.2)	61	68.9 (12.0)	51	67.6 (12.9)	61	69.0 (12.5)	51	G: ns T: ns GxT: ns
Symbol Search	30.4 (6.3)	61	30.2 (5.1)	51	30.8 (6.8)	61	30.3 (5.0)	51	G: ns T: ns GxT: ns
Trails A	28.2 (8.9)	61	27.2 (8.8)	51	27.4 (9.0)	61	26.6 (7.4)	51	G: ns T: ns GxT: ns
<u>Verbal Learning and Memory</u>									
CVLT, List A Trial 1	7.2 (2.2)	61	6.1 (1.3)	51	7.3 (2.1)	61	7.3 (2.2)	51	G: ns T: ns GxT: p = .02
CVLT, Long-Delay Free	12.5 (2.9)	61	12.1 (2.7)	50	13.2 (2.5)	61	12.8 (2.4)	51	G: ns T: ns GxT: ns
CVLT, Long-Delay Recog	29.4 (3.0)	60	29.2 (2.7)	50	29.9 (3.0)	61	29.2 (2.8)	51	G: ns T: ns GxT: ns

Logical Memory II	26.8 (6.8)	60	23.6 (7.2)	51	30.2 (5.7)	61	27.3 (7.0)	53	G: $p = .007$ T: ns GxT: ns
<u>Visual Learning and Memory</u>									
RVLT, Trial 1	4.6 (1.5)	61	4.1 (1.5)	51	5.0 (1.7)	61	4.9 (1.9)	51	G: ns T: $p < .0001$ GxT: ns
RVLT, Long-Delay Free	8.0 (2.3)	61	7.4 (2.5)	51	8.6 (2.4)	61	8.3 (2.5)	51	G: ns T: ns GxT: ns
RVLT, Long-Delay Recog	13.1 (1.1)	61	12.5 (1.4)	51	13.1 (1.4)	61	13.2 (1.2)	51	G: ns T: ns GxT: $p = .02$
Family Pictures II	45.1 (9.1)	60	41.7 (9.5)	50	46.1 (9.3)	61	46.9 (8.7)	50	G: ns T: $p < .0001$ GxT: $p = .013$
<u>Visuospatial Function</u>									
Block Design	36.1 (11.1)	61	33.8 (10.0)	51	37.0 (11.4)	61	34.5 (10.5)	51	G: ns T: ns GxT: ns
<u>Working Memory</u>									
Arithmetic	14.0 (3.4)	60	13.8 (3.0)	51	14.3 (3.3)	60	13.8 (3.1)	51	G: ns T: ns GxT: ns
CCC Total	43.1 (7.2)	57	42.9 (7.1)	50	43.0 (8.4)	57	45.0 (7.6)	49	G: ns T: ns GxT: ns
Digit Span (F & B)	17.0 (4.3)	60	17.2 (4.2)	50	17.2 (4.0)	61	18.3 (3.6)	51	G: ns T: ns GxT: ns
Letter-Number-Sequencing	10.7 (2.7)	61	10.5 (2.2)	51	10.3 (2.6)	61	11.0 (2.2)	51	G: ns T: ns GxT: $p = .03$
Spatial Span	15.2 (2.6)	61	15.2 (2.5)	51	15.4 (2.7)	61	15.5 (2.5)	51	G: ns T: ns GxT: ns

Notes: SD= standard deviation; G = Group; T = Time; GxT = Group x time interaction;

ns = non-significant.

Table 13. Unadjusted means and standard deviations on POMS subscales for chemotherapy and hormonal groups, and results of ANOVAs and ANCOVAs on these measures.

POMS Measure	Time 1				Time 2				Significance
	Chemo Mean (SD)	n	Hormonal Mean (SD)	n	Chemo Mean (SD)	n	Hormonal Mean (SD)	N	
Depression-Dejection	8.5 (9.3)	60	5.0 (6.4)	51	6.2 (9.4)	61	5.6 (7.1)	51	G: ns T: ns GxT: p = .05
Fatigue-Inertia	7.8 (6.9)	60	8.2 (5.8)	51	10.7 (7.1)	62	9.0 (7.1)	51	G: ns T: p = .005 GxT: ns
Tension-Anxiety	11.2 (6.7)	60	8.8 (6.4)	51	7.9 (6.6)	61	8.3 (6.5)	51	G: ns T: p = .005 GxT: ns

Notes: POMS = Profile of Mood States.³³ SD= standard deviation.

IQ, disease stage, inter-test interval, or change in POMS depression or anxiety. The non-decliners actually showed a greater increase in fatigue from T1 to T2 than the decliners. Decliners had less education than non-decliners ($p = .03$) and were more likely to be on antidepressant medication at baseline ($p = .05$).

In terms of individual cognitive measures, frequency of decline was greater in the chemotherapy group than in the hormonal group on CCC Total ($\chi^2 = 5.4$, $p = .02$), WCST Trials Administered ($\chi^2 = 4.3$, $p = .04$), and Digit Span ($\chi^2 = 3.8$, $p = .05$).

Cognitive Domain Summary Scores

The Working Memory Composite Score was lower in the chemotherapy group than the hormonal group ($t = -2.2$, $p = .03$). There were no group differences in the other cognitive domain composite scores.

Three-Group Comparisons

All analyses were repeated including the healthy control group. Their demographic information is presented in Table 14; their means and standard deviations on the 23 cognitive measures and the results of the three-group ANOVAS and ANCOVAS are in Table 15. There was a tendency for the healthy control group to have higher IQ and education than the patient groups. There were six significant group-by-time interactions in the univariate ANOVAs/ANCOVAs on the neuropsychological measures. Pairwise interactions revealed that these effects were primarily due to less improvement on measures of memory and working memory in the chemotherapy group compared to the hormonal group. In this three-group model, in which SRB change scores were referenced to the healthy controls, 51% (31 of 61) of the chemotherapy subjects, 41% (21 of 51) of the hormonal subjects, and 11% (3 of 28) of the normal controls showed reliable cognitive decline ($\chi^2 = 13.1, p = .001$). The two patient groups differed from the healthy controls, but not from each other. There were no group differences in frequency of reliable cognitive improvement (11% in chemotherapy group, 10% in hormonal group, 4% in healthy controls; $p = .49$).

Among the domain-specific summary scores, significant effects of group were obtained for Processing Speed ($p = .01$), Verbal Memory ($p = .04$), Visual Memory ($p = .01$), and Working Memory ($p = .004$). These were generally due to lower scores in one or both of the treatment groups compared to the healthy control group. However, the Working Memory Summary Score was significantly lower in the chemotherapy group than in both the healthy control group ($p = .01$) and the hormonal group ($p = .003$).

Table 14. Demographic and clinical characteristics of healthy control participants.

Characteristic	N=28
Age (in years at baseline)	
Mean (SD)	59.3 (4.2)
Min/Max	51-66
Education (in years at baseline)	
Mean (SD)	15.9 (2.5)
Min/Max	12-21
Estimated verbal IQ (at baseline)	
Mean (SD)	112.2 (10.3)
Min/Max	96-135
Test-retest interval (in days)	
Mean (SD)	151.9 (30.1)
Min/Max	98-218
Proportion on depression meds (at baseline)	3.7% (n=1)

Notes: SD= standard deviation; IQ= intelligence quotient as

measured by the Quick Test (Ammons & Ammons, 1962).

Table 15. Unadjusted means and standard deviations on the cognitive measures for healthy control subjects, and results of three-group (chemotherapy, hormonal therapy, and healthy) ANOVAs and ANCOVAs on these measures.

Cognitive domain/Measure	Time 1		Time 2		Significance
	Mean (SD)	n	Mean (SD)	n	
<u>Executive function</u>					
PASAT, 2.4s, total correct	41.8 (8.2)	23	47.1 (7.3)	23	G: ns T: ns GxT: ns
Trails B	65.2 (15.8)	28	59.8 (15.9)	28	G: ns T: ns GxT: ns
WCST, Trials administered	93.8 (22.4)	27	92.3 (23.7)	27	G: ns T: ns GxT: ns
<u>Language</u>					
Boston Naming Test, total	56.9 (3.0)	28	57.8 (2.5)	28	G: ns T: ns GxT: ns
FAS, total correct	43.1 (13.5)	28	44.4 (11.6)	28	G: ns T: ns GxT: ns
<u>Motor</u>					
Grooved Pegboard, D & ND	145.5 (20.5)	28	148.8 (25.3)	28	G: ns T: ns GxT: ns
<u>Processing Speed</u>					
Digit-Symbol Coding	72.3 (11.3)	28	75.6 (10.2)	28	G: ns T: ns GxT: ns
Symbol Search	30.5 (5.9)	28	32.1 (5.3)	28	G: ns T: ns GxT: ns
Trails A	25.3 (5.4)		25.1 (5.4)		G: ns T: ns GxT: ns
<u>Verbal Learning and Memory</u>					

CVLT, List A Trial 1	6.8 (1.7)	28	8.5 (2.4)	24	G: p = .02 T: ns GxT: p = .007
CVLT, Long-Delay Free	13.5 (2.1)	28	14.5 (1.6)	28	G: ns T: ns GxT: ns
CVLT, Long-Delay Recog	30.3 (2.1)	28	30.4 (2.1)	28	G: ns T: ns GxT: ns
Logical Memory II	29.6 (7.2)	28	32.7 (7.2)	28	G: p = .003 T: ns GxT: ns
<u>Visual Learning and Memory</u>					
RVLT, Trial 1	5.4 (1.7)	28	6.1 (1.8)	28	G: p = .001 T: p < .0001 GxT: ns
RVLT, Long-Delay Free	8.9 (2.5)	28	9.6 (2.2)	28	G: ns T: ns GxT: ns
RVLT, Long-Delay Recog	13.1 (1.2)	28	13.5 (1.1)	28	G: ns T: p = .05 GxT: p = .03
Family Pictures II	42.9 (9.4)	28	48.7 (7.0)	28	G: ns T: ns GxT: p = .008
<u>Visuospatial Function</u>					
Block Design	38.6 (10.5)	28	40.1 (9.9)	28	G: ns T: ns GxT: ns
<u>Working Memory</u>					
Arithmetic	15.5 (2.9)	28	15.8 (2.9)	28	G: ns T: ns GxT: ns
CCC Total	42.9 (7.1)		51.3 (5.1)		G: p = .002 T: ns GxT: p = .03
Digit Span (F & B)	18.1 (3.9)	28	17.6 (3.5)	28	G: ns T: ns GxT: ns
Letter-Number-Sequencing	10.4 (2.6)	28	11.3 (2.5)	28	G: ns T: ns GxT: p = .01

Spatial Span	15.5 (2.3)	28	15.4 (2.5)	28	G: ns
					T: ns
					GxT: ns

Notes: SD= standard deviation; G = Group; T = Time; GxT = Group x time interaction.

As in the two-group model, there were no differences between those chemotherapy patients who declined and those who did not in terms of chemotherapy regimen, number of cycles, age, disease stage, inter-test interval, or change in POMS anxiety. The non-decliners again showed a larger increase in fatigue from T1 to T2 than the decliners. The non-decliners also showed a lesser reduction in depression scores than the decliners. However, the decliners had significantly higher baseline depression scores ($p=.035$) and were more likely to be on depression medications at T1 ($p=.051$). The decliners were again found to have less education than the non-decliners ($p=.001$) and in this model, they had lower IQ as well ($p<.0001$).

DISCUSSION

We attempted to bring greater clarity to the topic of “chemo fog” by conducting a prospective cohort study. Little effect of chemotherapy was found when data were analyzed at the aggregate level. Even after treatment, all group means were within the normal range relative to published norms. Any group-level changes in scores from baseline to retest, even in our chemotherapy subjects, were positive, indicating better performance at retest than at baseline. There were greater practice effects in the hormonal subjects than the chemotherapy subjects on select measures of memory and working memory. However, these interaction effects were small and would not have been significant had we corrected for overall Type I error rate. Furthermore, the hormonal

group scored lower than the chemotherapy group at baseline on many of these measures, so this may simply have been a result of regression to the mean.

When analyzing individual change, we did observe a greater risk of cognitive decline in the chemotherapy compared to the hormonal patients (26% and 8%, respectively), even after statistically accounting for age, intelligence, fatigue, psychological distress, and regression to the mean. However, when change scores for both the hormonal and chemotherapy groups were referenced to healthy controls, an increased and approximately equal risk of cognitive decline was observed in both patient groups. This suggests that any specific effect of chemotherapy on cognition is extremely subtle, and is eclipsed by other factors affecting cancer patients.

These results underscore the importance of study design. A controlled prospective approach is essential to studies in this area. The within-subjects component permits the evaluation of individual change in relation to treatment; the between-subjects component provides a means of accounting for practice effects that could obscure subtle losses in a pure within-subjects design. The choice of control group is also critical, as demonstrated by the fact that the greater risk of cognitive decline in the chemotherapy group relative to the hormonal group observed in two-group analyses was not evident when both patient groups were referenced to healthy subjects. Hormonal treatment (Bender et al., 2006; Castellon et al., 2004; Eberling et al., 2004; Shilling et al., 2003) as well as radiation-induced fatigue (Bower et al., 2006; de Jong, Candel, Schouten, Abu-Saad, & Courtens, 2004) may themselves have adverse effects on cognition. It is possible that these competing treatment effects, more likely in the hormonal group than the chemotherapy group, resulted in an underestimation of the cognitive effects of chemotherapy and reduced the likelihood of finding a significant difference between the patient groups, especially

when the data were analyzed from the broader perspective of the three-group model. Finally, the manner in which “reliable decline” is defined will greatly influence the outcome of studies such as this one (Shilling et al., 2006). We defined reliable cognitive decline as a change score greater than or equal to 2 standard deviations below the reference group on 2 or more of our 23 cognitive measures. This criterion was selected because a) 2 standard deviations below the mean of a normal control group is conventionally used to define impairment in clinical neuropsychological practice and b) reliable cognitive decline so-defined occurred infrequently in the healthy control group. Although the stringency of the decline criterion will have a profound effect on the rate of decline observed *within* a given group, it cannot as easily account for significant group differences in rate of decline.

The fact that the cognitive effects of chemotherapy are so subtle raises the question as to their clinical significance. Experience with other neurological conditions such as sports-related concussion (Barth et al., 1983), HIV-1-Associated Mild Neurocognitive Disorder (Mendez & Cummings, 2003), and multiple sclerosis (Hannay, Howieson, & Loring, 2004) is perhaps relevant here. It was only with considerable refinement of assessment tools and study design that researchers were able to detect the subtle deficits in attention, processing speed, executive function, and memory underlying these patients’ cognitive complaints. Recent findings, including current observations that working memory measures were particularly sensitive to chemotherapy, suggest that chemo fog may have a similar neuropsychological profile (Shilling et al., 2005; Scherwath et al., 2006; Saykin et al., 2003). A recent fMRI study showed more diffuse brain activation in breast cancer patients exposed to chemotherapy than in controls during a working memory task, in the absence of any *performance* differences (Saykin et al., 2006). These changes

in brain activation may reflect a brain mechanism for compensating for subtle dysfunction, and may underlie patients' experience of cognitive disturbance.

There has been considerable speculation in the literature as to the mechanism of chemotherapy-related cognitive dysfunction. Fatigue, psychological distress, and changes in endocrine status are often proposed as mediating factors. In our study, the chemotherapy patients did show a significant increase in fatigue after therapy compared to the hormonal subjects. However, within the chemotherapy group, the decliners showed less increase in fatigue than the non-decliners. The decliners also tended to show greater reduction in depression scores after treatment than the non-decliners. However, they did have significantly higher baseline depression scores and were more likely to be on depression medications at study outset suggesting that stress tolerance may be a risk factor for chemo fog. It would be interesting to evaluate this and other personality constructs as risk factors in future studies. Changes in menopausal status clearly do not explain our findings given that all subjects were postmenopausal at study outset.

We also failed to find differences between *decliners* and *non-decliners* in the chemotherapy group on a number of other putative risk factors, including age, disease stage, test-retest interval, chemotherapy regimen, and number of cycles. The two groups did differ on education, such that lower levels of education seemed to be a risk factor. Lower education was also a risk factor for cognitive decline in the hormonal group. It has been posited that more educated people have greater "cognitive reserve" and can better tolerate brain insult without manifesting cognitive symptoms (Stern, 2002). The fact that this effect was evident in a fairly educated sample suggests that we might see a more pronounced effect of these treatments in a less educated group.

In conclusion, results of this study are consistent with the emerging view that chemotherapy exposure is associated with cognitive changes, but that these are extremely subtle. Refinement of assessment tools and study design is necessary to improve our understanding of this subtle and complex phenomenon. This, in turn, will allow treating professionals to offer appropriate education, support, and intervention to those individuals who may experience distressing cognitive side effects of their cancer treatments.

GENERAL DISCUSSION

The purpose of the work described in this thesis was to examine the phenomenon of chemo fog. This was first accomplished by conducting a quantitative review of the literature using a meta-analytic approach. The second part entailed the collection of neuropsychological data from two groups of breast cancer patients and a smaller group of healthy women at two time points. These two studies were presented in the form of two journal articles.

This discussion is divided into four sections. The first section briefly summarizes the results obtained from the meta-analysis. An expanded discussion of the findings and implications of Study 2 is presented in the second section. The third section of the discussion seeks to broaden our understanding of the topic of chemo fog by examining the effect of chemotherapy and other similar treatments in other types of cancer. The final section examines the various limitations of this work and provides considerations for future research.

Study 1

In Study 1, “A meta-analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer”, the objective was to estimate the magnitude of neuropsychological decline among early stage breast cancer patients treated with adjuvant chemotherapy. Combining data from six cross-sectional studies and a single prospective study, results revealed significantly lower test scores among breast cancer patients exposed to adjuvant chemotherapy than for the groups with which they

were compared. Neuropsychological test scores were approximately one-quarter to one-half a standard deviation below comparison levels on most cognitive domains, with an overall effect size of -0.26 . Although the increase in power afforded to meta-analytic techniques boosted the likelihood of obtaining significant group differences, the results also underscored the subtle nature of this phenomenon. While this meta-analysis served to provide an overall estimate of the size of expected cognitive decline in breast cancer patients exposed to adjuvant chemotherapy, it did not consider the all-important impact of study design (e.g., prospective versus retrospective design).

Study 2

The aim of the second article, “The cognitive effects of adjuvant chemotherapy in early stage breast cancer: A prospective study” was to shed light on the topic of chemo fog by addressing several methodological weaknesses. Some of the concerns surrounding this topic were due to the retrospective nature and lack of a comparison group in many previous studies (Ahles & Saykin, 2001; Ahles & Saykin, 2002; Rugo & Ahles, 2003). This study included a pre-treatment baseline assessment of cognitive function that would allow for a monitoring of cognitive change on an individual basis and also included a control group of cancer patients, similar to our chemotherapy patients, who received hormonal therapy only. Given concerns that the neuropsychological decline associated with chemo fog may be due to a lack of improvement in the form of practice effects (Fan et al., 2005), we also included a sample of healthy women to gauge the extent of improved performance as a result of repeated neuropsychological assessment.

In this study, no mean score on any cognitive measure, in any group, at either baseline or retest fell outside the normal range as compared to published norms. When

change was evaluated on an individual basis, there was a modest but significantly greater risk of cognitive decline in the chemotherapy group (26%) relative to the hormonal participants (8%). Shortly after completion of chemotherapy treatment, patients exposed to chemotherapy were 3.3 times more likely to experience reliable cognitive decline compared to hormonal participants. These findings were in keeping with the prospective study by Shilling et al. (2005) who reported a 2.25 fold increase in the risk of cognitive decline among patients exposed to chemotherapy in the acute phase of their illness.

However, when change scores for both the hormonal and chemotherapy groups were referenced to a small sample of healthy control participants, the difference in frequency of cognitive decline between the treatment groups (chemotherapy and hormonal) disappeared. In this three-group model, an increased and approximately equal risk of cognitive decline was observed in both treatment groups due to the fact that healthy controls were much more different than either chemotherapy or hormonal patients. This suggests that any specific effect of chemotherapy on cognition is extremely subtle and is eclipsed by other factors associated with being a cancer patient. The fact that there is a nonspecific association between breast cancer and cognition probably explains why retrospective cross-sectional studies typically yield much larger effect sizes than do prospective within-subject designs (Falleti et al., 2005) and underscores the critical nature of study design when investigating the subtle and complex phenomenon of “chemo fog”.

It is a subset of women who appear to be vulnerable to chemo fog. Some estimates found 25% to 30% of breast cancer patients exposed to adjuvant chemotherapy experienced cognitive decline (Schagen et al., 1999; Shilling et al., 2005). While the findings of both studies presented in this thesis do not conflict with this conclusion, a consideration of base rates does lower this estimate. The frequency of reliable neuropsychological decline of

control participants provides an indication of base rates. In the two-group model, 6% of hormonal participants met the criterion for reliable cognitive loss. Thus, the 26% of chemotherapy patients found to show reliable cognitive decline could be reduced by up to 6% to reflect base rate conditions. Overall, base rates have not been taken into account in this research area, leading to a small overestimation of the true iatrogenic effects of adjuvant chemotherapy. Even so, the sheer incidence of this disease ensures that this problem afflicts a sizeable number of women each year. As the threshold for recommending adjuvant chemotherapy for early stage breast cancer patients continues to decrease (Harlan et al., 2006; Piccart et al., 2005), the incidence of chemo fog is likely to increase.

The fact that chemo fog is not a universal experience makes the identification of specific disease-, host-, or treatment-related factors related to this vulnerability of considerable value. In the subgroup of chemotherapy participants who showed reliable cognitive decline, use of anti-depressant medication and lower education at baseline was found to be a risk factor. To our knowledge, this is the first study to identify use of anti-depressant medication at baseline as a risk factor for developing chemo fog. It may be that adjustment difficulties to a cancer diagnosis and associated treatment may result in a susceptibility to chemo fog. With regard to lower education as a risk factor, while Study 2 highlighted the cognitive reserve hypothesis (Stern, 2002), an alternative explanation is that there is a ceiling effect on some of the measures, such that more educated women can maintain their scores despite cognitive decline. Unlike other studies (Ahles et al., 2002; Schagen et al., 1999; van Dam et al., 1998), we did not find either chemotherapy regimen or number of chemotherapy cycles to be associated with cognitive decline in our sample. This may be due to the homogeneity of our chemotherapy group and the treatments that

they received. On the other hand, this may also speak to a non-specific aspect of chemotherapy such that if it or its metabolites are able to cross the BBB, there is a chance for brain insult.

While results from our meta-analysis and that of several other studies and reviews in the area pinpoint chemo fog as a global phenomenon affecting diffuse brain activity (Ahles & Saykin, 2001; Schagen et al., 1999; Wieneke & Dienst, 1995), results of Study 2 found working memory to be particularly susceptible to the iatrogenic effects of adjuvant chemotherapy. Shilling et al. (2005) also reported a similar finding. Working memory capacity is considered to be one of the first cognitive functions to break down in many brain disorders, including mild traumatic brain injury (Lezak et al., 2004) and thus this result is not overtly surprising. Working memory tasks are sensitive to white matter disease and there is some evidence to suggest that white matter may be sensitive to the toxic effects of adjuvant chemotherapy (Choi et al., 2001). While our study and that of Shilling et al. (2005) isolated the subtle decline to working memory tasks, it is worthwhile to bear in mind that of the cognitive domains, working memory is considered to involve multiple brain areas and is thus in many ways emblematic of diffuse brain dysfunction. Although a comprehensive battery assessing all cognitive domains is recommended, the necessity for brief cognitive batteries such as in the case of clinical trials may place an emphasis on working memory measures.

While the frequency of cognitive decline was significantly greater in the chemotherapy group compared to the hormonal group, this was a statistical difference only and does not inform us as to the clinical utility of this finding. Breast cancer patients have described a cluster of symptoms associated with chemo fog, including difficulties in completing multiple tasks at the same time (Tannock et al., 2004) and a kind of mental

fogginess (Schagen et al., 2002). Such descriptions although useful, remain vague, and difficult to interpret in terms of their impact on daily life. Jenkins et al. (2006) failed to find a relationship between those who experienced chemo fog and any changes in quality of life. Falleti et al. (2005) provided an insightful analogy of what it may be like to suffer from chemo fog. Studying the cognitive effects of fatigue on healthy adults, this research group found that being continuously awake for 12 hours was equivalent to a 0.3 effect size reduction in cognitive status (Maruff et al., 2005). Falleti et al. (2005) thus suggested that the cognitive decline associated with adjuvant chemotherapy is similar to that experienced by fatigue at the end of a normal day. One only has to imagine how one feels at the end of a working day to appreciate the extent of cognitive decline and its potential impact on return to work or school and more broadly speaking, personal life issues.

Much like the incongruity between cognitive decline and quality of life, there has been a lack of a relationship between objective and subjective measures of cognitive function in chemotherapy patients (Ahles et al., 2002; Castellon et al., 2004; Donovan et al., 2005; Jenkins et al., 2006; Schagen et al., 1999; Schagen et al., 2001; van Dam et al., 1998). The fact that any chemotherapy-related cognitive change is subtle and that cross-sectional studies cannot capture individual change, may help explain the discrepancy between subjective and objective measures of cognitive function. A woman with high premorbid cognitive function could well experience troubling cognitive decline over the treatment period, yet still score within normal limits in relation to published peer norms on standardized psychometric tests. It is only by examining change scores that the subjective experience of cognitive loss would be corroborated. This being said, we found no interpretable correlations between changes in cognitive scores and self-reported changes in

confusion as measured by the POMS, an instrument that measures mood and affective states.

The lack of a relationship between objective and subjective findings may also be explained by the insensitivity of either neuropsychological (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005) or self-report measures. For instance, of the 18 neuropsychological measures administered in the current study, only 3 tests (CCC Total [Brown, 1958], Digit Span, Wisconsin Card Sorting Test, Trials Administered) differentiated the chemotherapy and hormonal groups on the basis of frequency of cognitive decline. Preliminary work conducted with fMRI have shown that even when no differences in working memory can be detected at a performance level, more diffuse brain activation can be detected in breast cancer patients exposed to chemotherapy (Saykin et al., 2006). This was interpreted as a compensatory mechanism and speaks to the subtlety with which some breast cancer patients experience chemo fog.

Cognitive complaints have been found to correlate better with measures of psychological distress than with objective cognitive measures in cross-sectional studies (Castellon et al., 2004; Jenkins et al., 2006; Shilling et al., 2005) and has been posited to suggest a functional rather than organic cause. Results from Study 2 found very little correlation between performance on neuropsychological tests and self-ratings of depression and anxiety as measured by the POMS and BDI-II. Indeed, at the group level, chemotherapy participants showed a trend toward greater improvement in mood and anxiety than hormonal control participants from first to second testing session.

Of the four prospective investigations completed to date (Bender et al., 2006; Hurria et al., 2006; Jenkins et al., 2006; Shilling et al., 2005; Wefel, Lenzi, Theriault, Davis et al., 2004), the results of Study 2 are at most odds with the findings and conclusion of Jenkins et

al.. This is somewhat surprising given the striking similarities in study design (nature of the comparison groups, timing of testing, selection of neuropsychological measures, approach to statistical analysis). Jenkins et al. (2006) have argued that lack of rigor in defining cognitive decline may have resulted in inflated rates of decline in other studies and to unfounded concerns about the negative impact of chemotherapy on cognition. In fact, they have demonstrated, by applying different criteria to their longitudinal data, how the definition of cognitive impairment can lead to very different conclusions (Shilling, Jenkins, & Trapala, 2006). It seems unlikely that this accounts for the discrepancy between our results and theirs, given that we have adopted a very similar definition of reliable cognitive decline. Moreover, cognitive decline, as we have defined it, was an infrequent occurrence in our group of hormonally treated patients (6%) in the two-group model or when referenced to the healthy controls (11%) in the three-group model.

The important difference between our study and that of Jenkins et al. is the fact that we included only post-menopausal women. As a result, our chemotherapy sample was somewhat older than theirs (57.5 years versus 51.5 years, respectively), with less variability in age. This raises the possibility that older, post-menopausal women may be more susceptible to the neurotoxic effects of chemotherapy than younger women. Although previous studies have generally not found age and menopausal status to predict risk of cognitive decline in chemotherapy treated breast cancer patients (Tchen et al., 2003; Shilling et al., 2005), most of these studies were not powered to examine these relationships. Jenkins et al. (2006) did find that those women in their sample who were rendered menopausal by their chemotherapy were more likely to show cognitive decline after treatment. Although it is generally accepted that elderly patients are much more susceptible to the side effects of many drugs (Howieson et al., 2004), Hurria et al. (2006)

prospectively examined the cognitive function of adults 65 years and older receiving adjuvant chemotherapy and found the frequency of reliable cognitive decline to not be any greater than that found among younger participants.

As highlighted by Study 2, the importance of study design including consideration of a prospective versus retrospective approach, choice of a control group, influence of commonly prescribed hormonal treatment, impact of radiation-induced fatigue, and differences in the definition of reliable cognitive decline can lead to different conclusions with respect to the nature and severity of chemo fog. Because the choice of the control group in the current study gave rise to significantly different results, a discussion of the optimal control group against which to gauge the extent of chemotherapy-induced cognitive decline is further explored here. Because this is the first time that individual change scores have been analyzed using an advanced SRB approach, the concerns and benefits of this technique are also discussed.

Variation among studies in the choice of a control group has probably contributed to the difference in magnitude of effects from one study to another (Shilling et al., 2006). While it is not possible to exactly match control subjects to chemotherapy subjects on disease severity in a study where patients are not randomized to treatment, we attempted to match our groups as closely as possible on several variables (such as age and menopausal status), ones that may have exaggerated group differences in other studies. Although many of the women in our chemotherapy group (those with ER+ tumors) were scheduled to receive hormonal treatment in conjunction with adjuvant chemotherapy, due to changes in international treatment guidelines (Albain et al., 2004 as cited in Early Breast Cancer Trialists' Collaborative Group, 2005), the majority of them had not yet commenced their hormonal treatment by the second assessment. There is evidence to suggest that hormonal

therapy may itself have a negative impact on cognition (Bender et al., 2006; Castellon et al., 2004; Eberling et al., 2004; Jenkins et al., 2004; Paganini-Hill et al., 2000; Shilling et al., 2003). Thus if anything, use of the hormonal group as a reference group may have resulted in an underestimation of the iatrogenic effects of chemotherapy treatment due to the possible competing detrimental effects of hormonal treatment on cognition. Although not part of this thesis, the long-term follow-up of these participants will shed light on whether or not hormonal treatment contributes an additive effect to cognitive decline.

The importance of using a prospective design in investigating chemo fog has been established (Olin, 2001). Along with serial cognitive assessment comes the need to take into account the potential confounding effects of practice. Most prospective studies have dealt with this by using a modified version of the reliable change index technique (e.g., Shilling et al., 2005; Wefel, Lenzi, Theriault, Davis et al., 2004). While this method is relatively simple to carry out, it does not allow for the consideration of other potentially confounding factors such as regression to the mean and the statistical control of potential covariates. We employed the SRB approach that offered vastly greater flexibility in being able to not only account for practice effects, but also regression to the mean and potential covariates. This was a multi-step process that involved the identification of possible covariates, running regression analyses for each of the 23 neuropsychological measures, computation of change scores, and tally of reliable cognitive decline for each subject. Similar to Jenkins et al. (2006), we found education and IQ to be important predictors of cognitive performance. While the SRB method is a time-consuming process, the ability to statistically control for practice effects, regression to the mean, and basic characteristics (e.g., education) known to highly influence neuropsychological test scores is especially

relevant to this topic given that the observed effects of chemo fog are considered to be at best, subtle in nature.

Neuropsychological impact of chemotherapy treatments on other cancers

The neuropsychological sequelae of chemotherapy and other treatments have been studied in various cancer populations. While much remains to be learned, it is worthwhile to address the cognitive effects of chemotherapy as treatment for breast cancer within the broader context of other types of cancer and cancer therapies. Beginning with childhood cancers, various kinds of disease are briefly reviewed with the exception of central nervous system tumors and their specific treatments (e.g., whole brain irradiation) where cognitive deficits may be more likely to occur (Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Twijnstra, Boon, Lormans, & Ten Velde, 1987).

Initial interest on this topic was due to concerns over the neuropsychological impact of treatment for childhood cancers. Although the effects of chemotherapy on the developing brain are thought to be qualitatively distinct from those on the adult brain (Anderson-Hanley et al., 2003; Jansen et al., 2005), there are some similarities. The single most striking resemblance is found in the pattern of neuropsychological loss.

Chemotherapy for the treatment of many childhood cancers has *not* revealed obvious cognitive problems (Butler, Hill, Steinherz, Meyers, & Finlay, 1994), perhaps due to the plasticity of the developing brain.

When considering the neuropsychological sequelae of breast cancer, an obvious comparison may be to look at the most common form of cancer in men, that being prostate cancer. Prostate cancer has a high incidence rate, is usually detected early, has a very good prognosis, and is often fueled by sex hormones, testosterone in this case (Canadian Cancer

Society, 2006). Standard treatment for early stage prostate cancer comprises surgery (prostatectomy), radiation therapy, and hormonal therapy to the exclusion of chemotherapy (Canadian Cancer Society, 2006). Thus, knowledge related to the neuropsychological effects of prostate cancer and its treatment is essentially limited to the effects of hormonal treatment.

The goal of hormonal treatment in prostate cancer is to render circulating serum testosterone levels similar to those had castration occurred. This is commonly referred to as androgen deprivation therapy. Duration of this type of treatment is between three months to three years or more (Salminen et al., 2003). Interestingly, testosterone is intricately connected to estrogen. In the brain, testosterone is converted to estrogen (Gouchie & Kimura, 1991). A lack of neural testosterone is associated with small cognitive decline in the areas of reduced reaction time, attention, and spatial memory (Jenkins, Bloomfield, Shilling, & Edginton, 2005; Salminen, Portin, Koskinen, Helenius, & Nurmi, 2004; Salminen, Portin, Koskinen, Helenius, & Nurmi, 2005), although this has not been found consistently (Cherrier, Rose, & Higano, 2003; Shahinian, Kuo, Freeman, & Goodwin, 2006). These findings are in keeping with more recent evidence suggesting that hormonal therapy in the treatment for breast cancer has detrimental effects on cognition (Bender et al., 2006; Jenkins et al., 2006).

With respect to the neuropsychological effects of chemotherapy at other cancer sites, results are similar to that found in the breast cancer literature and generally suffer from the same methodological concerns. Jansen et al. (2005) conducted a meta-analysis of the effects of chemotherapy on several different types of cancer including breast cancer, various solid tumors, hematologic cancer, and lung cancer. When the results excluded breast cancer studies, the effect sizes remained in the small to medium size range. Similar

results have been also reported among a subgroup of patients with solid tumors (Meyers & Abbruzzese, 1992). While the administration of different chemotherapy regimens depends on the cancer site and disease severity, the fact that the iatrogenic effects of chemotherapy appear to span a wide variety of cancer types suggest that it is not any single chemotherapy agent or combination of agents that is the cause of cognitive disturbance. Although the impact of different chemotherapy regimens on neuropsychological function requires further study, it appears as though a simple shift in type of chemotherapy regimen is not likely to eliminate the problem of chemo fog.

Limitations and future directions

One of the main limitations of Study 2 concerns the composition of the adjuvant chemotherapy group. The chemotherapy group consisted of ER- patients who were not scheduled to receive hormonal therapy ($n = 20$), ER+ patients who had received hormonal treatment by the second assessment ($n = 12$), and other ER+ patients, who, due to changes in standards of care, were only scheduled to start hormonal therapy after the second assessment ($n = 29$). Considering that our primary reference group was breast cancer patients treated with hormonal therapy only, our decision to include ER- patients was a practical one. Knowing that our eligibility criteria (restrictions on age, disease severity, and menopausal status) would already reduce the recruitment pool, we opted to include ER- patients in the study. In future, perhaps a better control group for ER- patients treated with surgery and chemotherapy may be early stage breast cancer patients treated with surgery only. Based on the few prospective studies conducted to date, multicentre recruitment has been successful and appears to be a feasible option to reduce the overall recruitment period.

With regard to the change in standard of care for patients with ER+ tumors, obviously we could not alter the recommended treatment to patients for the benefit of our study.

The long-term follow-up of all breast cancer and healthy control subjects scheduled to take place approximately one-year after the short-term assessment is not part of this thesis and marks an important limitation. While the results of Study 2 support the notion of subtle cognitive decline in a subgroup of women exposed to adjuvant chemotherapy, the extent to which this neuropsychological detriment is persistent or possibly worsens over time are important questions that cannot be answered here. Among longitudinal prospective studies published to date, it appears that the frequency and magnitude of cognitive decline in the subgroup of breast cancer patients treated with adjuvant chemotherapy is not worsening as one would expect in a progressive illness like dementia. In fact, breast cancer patients' cognitive status generally improved or stayed the same at the long-term assessment (Jenkins et al., 2006).

When we initiated our study on the neuropsychological effects of adjuvant chemotherapy in newly diagnosed women with early stage breast cancer, there was very little information available on this topic. Since then, a plethora of cross-sectional studies has emerged and a handful of prospective studies have been published. The importance of determining the extent to which chemo fog persists over the long-term is an obvious and essential avenue for further inquiry. Additionally, all studies to date have excluded breast cancer patients with a previous history of cancer. While early stage breast cancer is highly treatable, a number of patients do experience a recurrence. In order to better counsel women as to what they may expect, it would be interesting to know whether prior chemotherapy exposure makes one more susceptible to cognitive loss following chemotherapy treatment for a recurrence.

Conclusion

In conclusion, this thesis employed both historical and original data to better understand the topic of chemo fog. The first study involved a meta-analysis of the available literature and found that a subgroup of breast cancer patients likely experience neuropsychological decline as a consequence of adjuvant chemotherapy treatment. The second study involved a prospective investigation of the short-term neuropsychological effects of adjuvant chemotherapy among a cohort of early stage breast cancer patients scheduled to receive either adjuvant chemotherapy, hormonal therapy alone, as well as a group of non-cancer, healthy controls. Results of the second study revealed that breast cancer patients treated with adjuvant chemotherapy were 3.3 times more likely to sustain subtle cognitive decline compared to breast cancer patients treated with hormonal therapy only. Risk factors among the subgroup of patients identified as exhibiting subtle cognitive loss were antidepressant medication at the baseline testing session and lower education. Although these results certainly suggest that chemotherapy is detrimental to neuropsychological function, when the two breast cancer groups were compared to their non-cancer, healthy counterparts, the harmful impact of adjuvant chemotherapy on cognitive function disappeared, suggesting that the influence of adjuvant chemotherapy is sufficiently subtle to be masked by other and as yet unknown factors associated with breast cancer. This raises the importance of study design and appropriate selection of a control group in the investigation of the phenomenon of chemo fog. Worthy avenues for further investigation include examining the longevity or persistence of chemo fog among patients exposed to adjuvant chemotherapy or with a prior history of chemotherapy.

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APPENDIX A

CONTRIBUTIONS OF THE COLLABORATORS

The conceptualization and design of Study 1, “A meta-analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer,” was a collaborative effort between myself and Dr. Bielajew. Collection and assembly of the data were executed by myself and Mr. Parkinson. I was responsible for the data analysis, interpretation, and preparation of the manuscript with editing contributed by Drs. Bielajew, Collins, and Tomiak.

Study 2, “The cognitive effects of adjuvant chemotherapy in early stage breast cancer: A prospective study” was a collaborative effort that included all authors to some extent. Data recruitment involved Ms. Mackenzie, myself, and Dr. Collins. Data collection principally included Ms. Mackenzie and myself. I was largely responsible for data analysis and manuscript preparation.

APPENDIX B
ETHICS APPROVAL

APPENDIX C

ADVERTISING MATERIALS



The Ottawa
Hospital | L'Hôpital
d'Ottawa

Canadian
Breast Cancer
Foundation
Ontario Chapter

Fondation
canadienne du
cancer du sein
Division de l'Ontario



Université d'Ottawa
University of Ottawa

BREAST CANCER PATIENTS NEEDED TO STUDY THE EFFECTS OF CHEMOTHERAPY ON MEMORY AND OTHER MENTAL FUNCTIONS

BESOIN PATIENTES AYANT REÇU UN DIAGNOSTIQUE DE CANCER DU SEIN, DANS LE BUT D'ÉtudIER L'EFFET DE LA CHIMIOThERAPIE SUR LA MÉMOIRE ET AUTRES FONCTIONS CÉRÉBRALES

ARE YOU ELIGIBLE ?

DO YOU HAVE A RECENT DIAGNOSIS OF BREAST CANCER ?

HAVE YOU NOT YET STARTED DRUG TREATMENT ?

ARE YOU A WOMAN BETWEEN THE AGE OF 50—65 ?

ETES-VOUS INTÉRESSÉ(E) ?

AVEZ-VOUS RÉCEMMENT REÇU UN DIAGNOSTIQUE DE CANCER DU SEIN ?

VOTRE TRAITEMENT N'A-T-IL PAS ENCORE DÉBUTÉ ?

ETES-VOUS UNE FEMME ENTRE 50 ET 65 ANS ?

If your answer to these questions is "YES," and you would be interested in participating,

Si vous avez répondu "OUI" à ces questions, et que vous êtes intéressé(e) de participer,

*Contact / Veuillez contacter : Dr. Barbara Collins at (613) 798-5555 ext. 13456
or Dr. Kate Bielajew at (613) 562-5800 ext. 4687*

Chemotherapy study Dr. Barbara Collins (613) 798-5555 ext. 13456 OR Dr. Kate Bielajew 613-562-5800 ext. 4687	Etude sur la chimiothérapie Dr. Barbara Collins (613) 798-5555 ext. 13456 OU Dr. Kate Bielajew 613-562-5800 ext. 4687
Chemotherapy study Dr. Barbara Collins (613) 798-5555 ext. 13456 OR Dr. Kate Bielajew 613-562-5800 ext. 4687	Etude sur la chimiothérapie Dr. Barbara Collins (613) 798-5555 ext. 13456 OU Dr. Kate Bielajew 613-562-5800 ext. 4687
Chemotherapy study Dr. Barbara Collins (613) 798-5555 ext. 13456 OR Dr. Kate Bielajew 613-562-5800 ext. 4687	Etude sur la chimiothérapie Dr. Barbara Collins (613) 798-5555 ext. 13456 OU Dr. Kate Bielajew 613-562-5800 ext. 4687



Are you interested in having your memory tested?

Are you a post-menopausal woman aged 50 – 65?

Then consider participating in our study

We are looking for healthy control subjects *without* cancer to study the effects of cancer treatments on memory and other mental functions. Control subjects are needed to assess the effects of repeated memory testing.

To be eligible to participate in the study, you:

- Must be willing to undergo tests of memory and other mental functions. This assessment lasts three hours and will be done at three different time points over an 18-month period. This testing can be performed in your own home or at The Ottawa Hospital and will be scheduled at your convenience.
- Must have no history of cancer
- Must be a minimum of one year post-menopausal
- Must be fluent in English

Written results will be provided at the completion of the study upon request.

For more information, please leave your name and phone number at

562-5800 ext. 4678

You will be promptly contacted for a brief telephone screening for eligibility.

Thank you for your interest.

This research study has been approved by The Ottawa Hospital Research Ethics Board



Aimeriez-vous faire évaluer votre mémoire?

***Êtes-vous une femme ménopausée âgée
de 50 à 65 ans?***

Si oui, pensez à faire partie de notre étude.

Nous sommes à la recherche de participantes en santé sans diagnostic de cancer pour nous aider à étudier les effets du traitement du cancer sur la mémoire et les autres fonctions cognitives. Les participantes contrôles comme vous nous aiderons à déterminer l'impact de faire évaluer sa mémoire à plusieurs reprises.

Pour être éligible, vous devez:

- Être prête à subir des tests de mémoire et d'autres fonctions cognitives. L'évaluation durera trois heures et sera répétée trois fois sur une période de 1.5 ans. L'évaluation peut être faite chez vous ou à L'Hôpital d'Ottawa selon votre préférence de journée et d'heure.
- Ne jamais avoir eu le cancer
- Être au moins un an passé votre ménopause
- Parler l'anglais couramment

Si vous le désirez, un sommaire écrit vous sera envoyé à la fin de l'étude.

Pour plus de renseignements, veuillez laisser votre nom et votre numéro de téléphone au

562-5800, poste 4678

Nous vous contacterons sous peu pour un bref questionnaire téléphonique afin de déterminer votre éligibilité.

Merci de votre intérêt.

Cette étude a reçu l'approbation du Conseil d'éthique en recherches de l'Hôpital d'Ottawa

APPENDIX D

INFORMATION SHEETS

(Breast cancer patient, English; Breast cancer patient, French;
Non-cancer, healthy control, English; Non-cancer healthy control, French)



INFORMATION SHEET

A Prospective, Longitudinal Study of the Neuropsychological and Psychosocial Effects of Cancer Therapy

PURPOSE OF STUDY

The current study is being carried out to explore the frequency, nature, and reasons for problems with mental functions (such as attention and memory) following chemotherapy and to determine the impact of these types of problems on day-to-day functioning and quality of life of cancer patients. We will therefore be testing people who are undergoing chemotherapy. We will also be testing breast cancer patients who are not receiving chemotherapy (who are receiving hormonal therapy such as Tamoxifen or Arimidex, or no systemic cancer treatment), in an effort to determine whether any changes we observe are due to chemotherapy specifically or to some other illness- or treatment-related factor. In addition, we will be testing a group of women without breast cancer for the purposes of determining how repeated testing affects scores on the tests being used to measure mental functioning.

INVESTIGATIONS

Participation in this study will involve pencil-and-paper tests of cognitive functioning (mental functions such as attention and memory), as well as questionnaires about mood, day-to-day functioning, and quality of life. These tests and questionnaires will be given on three separate occasions: before you begin chemotherapy, towards the end of chemotherapy, and one year after completion of chemotherapy (or at similar time points for those not receiving chemotherapy). This will allow us to determine whether any abnormalities in cognitive functioning are related to the chemotherapy, and whether they are transient or permanent. The psychological testing will take about three hours. The testing can be conducted at the hospital or at your home, whichever you prefer. If you choose to come to the hospital for your tests, your parking will be paid for.

RISKS

There are no particular risks associated with this psychological testing. Some people do experience performance anxiety in testing situations. Every effort will be made to alleviate this.

BENEFITS

There is no direct benefit to participants in this study other than the opportunity to learn more about their intellectual and psychological functioning. If you wish, you will be given feedback about this at the end of the study. The only other benefit to participants is the knowledge that they have contributed to our understanding of possible adverse effects of chemotherapy and to

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the quality of care available to future patients.

COMPENSATION

You will be paid \$50.00 for each of the testing sessions in which you participate to compensate you for your time.

QUESTIONS, WITHDRAWAL, AND CONFIDENTIALITY

Your participation in this study is entirely voluntary and, even if you decide to participate, you are free to withdraw at any time. If you choose not to participate or to complete the study, your decision will in no way affect your medical care at the Ottawa Hospital.

The information collected from you as part of this study will be held in the strictest confidence. Test forms will be identified by number--your name will not appear on them. Data from this study may be published but this data will not bear your name or any other identifying information.

If you have any questions or concerns about this research, or should you desire further explanation during the course of the study, you are encouraged to contact Dr. Barbara Collins, principal investigator, at 798-5555, ext. 13456, or Joyce MacKenzie, Research Associate, at 839-5438. You may also contact the Chairperson of the Ottawa Hospital Research Ethics Board at 798-5555, extension 14902 with any questions you may have about your rights as a research subject.

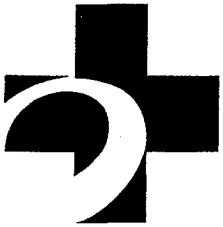
I understand the above information and voluntarily consent to participate in this study

Name

Signature

Date

Valid Until May 19, 2006



FEUILLE DE RENSEIGNEMENTS

Une Etude de L'Impact des Médicaments Utilisés dans le Traitement du Cancer sur les Fonctions Neuropsychologiques et l'Adaptation Psychosociale

BUT

Cette étude servira à explorer l'impact de la chimiothérapie sur le fonctionnement cognitif, les fonctions quotidiennes et la qualité de la vie chez les patients aux prises avec le cancer. Nous allons donc évaluer des patientes qui reçoivent des traitements de chimiothérapie. Nous verrons également des patientes qui ne reçoivent pas de chimiothérapie (celles qui reçoivent une thérapie hormonale telle que Tamoxifen ou Arimidex, ou qui ne reçoivent aucun traitement systémique) afin de mieux déterminer si les changements détectés sont reliés à la chimiothérapie ou à d'autres aspects du cancer et de son traitement. De plus, nous évaluerons un groupe de femmes non-atteintes du cancer du sein dans le but de déterminer l'impact que des évaluations répétées peuvent avoir sur les mesures cognitives.

INVESTIGATIONS

En acceptant de participer, vous acceptez de subir des évaluations psychométriques à trois reprises. L'évaluation psychométrique comprend des tests de mémoire, d'attention, de langage, etc., ainsi que des questionnaires de personnalité et de qualité de vie.

Ces investigations seront faites trois fois: avant de commencer la chimiothérapie, vers la fin de la chimiothérapie, et un an après avoir terminé la chimiothérapie. Cet horaire nous permettra de déterminer si des changements sont reliés à la chimiothérapie et s'ils sont temporaires ou permanents. L'évaluation psychométrique va prendre environ trois heures. Vous aurez le choix d'être évaluée chez vous ou à l'hôpital. Si vous décidez d'être évaluée à l'hôpital, nous nous ferons un plaisir de défrayer les coûts du stationnement.

RISQUES

L'évaluation psychométrique ne comportent pas de risque. Cependant, certaines personnes éprouvent de la nervosité lorsqu'elles sont évaluées. Nous ferons notre possible afin de minimiser une telle réaction.

BENEFICES

L'étude ne vous apportera aucun bénéfice direct autre que l'opportunité d'apprendre quelque chose au sujet de vos fonctions cognitives et psychologiques. Si vous le désirez, nous vous donnerons un résumé de vos résultats à la fin de l'étude. Vous aurez également la satisfaction d'avoir contribué à améliorer nos connaissances sur les effets cognitifs de la chimiothérapie et

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peut être d'avoir aidé à augmenter la qualité des soins de futur(e)s patient(e)s.

COMPENSATION

Afin de compenser pour votre temps, nous vous donnerons 50,00\$ pour chaque session d'évaluation à laquelle vous prendrez part.

QUESTIONS, REFUS DE CONTINUER, ET CONFIDENTIALITE

Votre participation est à titre bénévole seulement. Vous avez le droit de cesser de participer en tout temps même avant la fin des procédures. Votre refus de participer à cette étude n'entravera en rien les soins futurs que vous pourrez obtenir à l'Hôpital d'Ottawa.

Les renseignements obtenus lors de l'étude seront sauvegardés avec le plus de soin possible. Les tests psychométriques seront identifiés par un numéro et votre nom n'apparaîtra sur aucun des formulaires. Les données obtenues lors de cette étude pourront être publiées dans des revues scientifiques mais sans la publication d'aucun nom ou autre renseignement pouvant vous identifier.

Si vous avez des questions au sujet de cette recherche, n'hésitez pas à contacter le docteur Barbara Collins au 798-5555, ext. 13456, ou Joyce MacKenzie, associée en recherche, au 839-5438. Vous pouvez également contacter le Conseil d'éthique en recherches de l'Hôpital d'Ottawa au 798-5555, extension 14902 si vous avez des questions en ce qui concerne vos droits en tant que sujet de recherche.

Je comprends l'information ci-dessus et je consens volontairement à participer à cette étude.

Nom

Signature

Date

Valide jusqu'au 19 mai 2006



INFORMATION SHEET

A Prospective, Longitudinal Study of the Neuropsychological and Psychosocial Effects of Cancer Therapy

PURPOSE OF STUDY

The current study is being carried out to explore the frequency, nature, and reasons for problems with mental functions (such as attention and memory) following chemotherapy and to determine the impact of these types of problems on day-to-day functioning and quality of life of cancer patients. We will therefore be testing people who are undergoing chemotherapy. We will also be testing breast cancer patients who are not receiving chemotherapy (who are receiving hormonal therapy such as Tamoxifen or Arimidex, or no systemic cancer treatment), in an effort to determine whether any changes we observe are due to chemotherapy specifically or to some other illness- or treatment-related factor. In addition, we will be testing a group of women without breast cancer for the purposes of determining how repeated testing affects scores on the tests being used to measure mental functioning.

INVESTIGATIONS

Participation in this study will involve pencil-and-paper tests of cognitive functioning (mental functions such as attention and memory), as well as questionnaires about mood, day-to-day functioning, and quality of life. These tests and questionnaires will be given on three separate occasions: before you begin chemotherapy, towards the end of chemotherapy, and one year after completion of chemotherapy (or at similar time points for those not receiving chemotherapy). This will allow us to determine whether any abnormalities in cognitive functioning are related to the chemotherapy, and whether they are transient or permanent. The psychological testing will take about three hours. The testing can be conducted at the hospital or at your home, whichever you prefer. If you choose to come to the hospital for your tests, your parking will be paid for.

RISKS

There are no particular risks associated with this psychological testing. Some people do experience performance anxiety in testing situations. Every effort will be made to alleviate this.

BENEFITS

There is no direct benefit to participants in this study other than the opportunity to learn more about their intellectual and psychological functioning. If you wish, you will be given feedback about this at the end of the study. The only other benefit to participants is the knowledge that they have contributed to our understanding of possible adverse effects of chemotherapy and to

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the quality of care available to future patients.

QUESTIONS, WITHDRAWAL, AND CONFIDENTIALITY

Your participation in this study is entirely voluntary and, even if you decide to participate, you are free to withdraw at any time. If you choose not to participate or to complete the study, your decision will in no way affect your medical care at the Ottawa Hospital.

The information collected from you as part of this study will be held in the strictest confidence. Test forms will be identified by number--your name will not appear on them. Data from this study may be published but this data will not bear your name or any other identifying information.

If you have any questions or concerns about this research, or should you desire further explanation during the course of the study, you are encouraged to contact Dr. Barbara Collins, principal investigator, at 798-5555, ext. 13456, or Joyce MacKenzie, Research Associate, at 839-5438. You may also contact the Chairperson of the Ottawa Hospital Research Ethics Board at 798-5555, extension 14902 with any questions you may have about your rights as a research subject.

I understand the above information and voluntarily consent to participate in this study

Name

Signature

Date

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FEUILLE DE RENSEIGNEMENTS

Une Etude de L'Impact des Médicaments Utilisés dans le Traitement du Cancer sur les Fonctions Neuropsychologiques et l'Adaptation Psychosociale

BUT

Cette étude servira à explorer l'impact de la chimiothérapie sur le fonctionnement cognitif, les fonctions quotidiennes et la qualité de la vie chez les patients aux prises avec le cancer. Nous allons donc évaluer des patientes qui reçoivent des traitements de chimiothérapie. Nous verrons également des patientes qui ne reçoivent pas de chimiothérapie (celles qui reçoivent une thérapie hormonale telle que Tamoxifen ou Arimidex, ou qui ne reçoivent aucun traitement systémique) afin de mieux déterminer si les changements détectés sont reliés à la chimiothérapie ou à d'autres aspects du cancer et de son traitement. De plus, nous évaluerons un groupe de femmes non-atteintes du cancer du sein dans le but de déterminer l'impact que des évaluations répétées peuvent avoir sur les mesures cognitives.

INVESTIGATIONS

En acceptant de participer, vous acceptez de subir des évaluations psychométriques à trois reprises. L'évaluation psychométrique comprend des tests de mémoire, d'attention, de langage, etc., ainsi que des questionnaires de personnalité et de qualité de vie.

Ces investigations seront faites trois fois: avant de commencer la chimiothérapie, vers la fin de la chimiothérapie, et un an après avoir terminé la chimiothérapie. Cet horaire nous permettra de déterminer si des changements sont reliés à la chimiothérapie et s'ils sont temporaires ou permanents. L'évaluation psychométrique va prendre environ trois heures. Vous aurez le choix d'être évaluée chez vous ou à l'hôpital. Si vous décidez d'être évaluée à l'hôpital, nous nous ferons un plaisir de défrayer les coûts du stationnement.

RISQUES

L'évaluation psychométrique ne comportent pas de risque. Cependant, certaines personnes éprouvent de la nervosité lorsqu'elles sont évaluées. Nous ferons notre possible afin de minimiser une telle réaction.

BENEFICES

L'étude ne vous apportera aucun bénéfice direct autre que l'opportunité d'apprendre quelque chose au sujet de vos fonctions cognitives et psychologiques. Si vous le désirez, nous vous donnerons un résumé de vos résultats à la fin de l'étude. Vous aurez également la satisfaction d'avoir contribué à améliorer nos connaissances sur les effets cognitifs de la chimiothérapie et

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peut être d'avoir aidé à augmenter la qualité des soins de futur(e)s patient(e)s.

QUESTIONS, REFUS DE CONTINUER, ET CONFIDENTIALITE

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Je comprends l'information ci-dessus et je consens volontairement à participer à cette étude.

Nom

Signature

Date

Valide jusqu'au 19 mai, 2006

APPENDIX E

DESCRIPTION OF NEUROPSYCHOLOGICAL AND PSYCHOLOGICAL MEASURES

The following text describes the psychometric properties for the English versions of the neuropsychological tests only. Although it is recognized that equivalent Francophone tests may not have comparable psychometric properties, we did not want to exclude this group from opportunities to participate in research due to the importance of the Francophone community in this region. All tests were scored according to standard, manual instructions.

Estimate of intelligence

Quick Test

The Quick Test (Ammons & Ammons, 1962) is a brief screening tool of general intelligence (Swartz, 1984). This test is administered in less than ten minutes. The participant views plates containing four line drawings and indicates by pointing to the picture that most appropriately depicts the meaning of an orally presented word. The test contains 50 words; however, a typical administration involves only 15 to 20 items (Keyser & Sweetland, 1986). The test is discontinued once the participant reaches six successive failures. The total number of correct responses is easily converted to an IQ that has a mean of 100 and a SD of 15.

The Quick Test is positively related ($r = .64$) to the Full Scale IQ score of the Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981; Traub & Spruil, 1982) and measures of academic achievement (Marini, 1990; Violato, White, & Travis, 1984), thus supporting construct validity. Although considered a test of general intelligence, the Quick Test has been criticized as being primarily a measure of vocabulary and is only adopted

when time restraints forbid the administration of a full-scale individual intelligence test, as is the case in this study (Swartz, 1984).

Executive function

Paced Auditory Serial Addition Test

The Paced Auditory Serial Addition Test (Gronwall, 1977) is a challenging serial-addition task designed to measure the rate of information processing, as well as sustained and divided attention. It consists of a prerecorded tape of 61 numbers between one through nine in random order. The participant is asked to add two numbers with each number being added to the one that directly precede it. For a response to be recorded as correct, it must be given before presentation of the next number. This test includes four trials, each consisting of the same random sequence of 61 numbers. However, the rate of processing demands increase with each trial, as the speed of digit presentation is decreased (2.4, 2.0, 1.6, 1.2 seconds, respectively). Scoring consists of tallying the number of correct and incorrect additions per trial, with a maximum score of 60 per trial. It takes about 15 minutes to administer this test.

The Paced Auditory Serial Addition Test has high internal consistency as measured by split-half reliability (.96; Egan, 1988) and Cronbach's alpha (.90; Crawford, Obansawin, & Allan, 1998). McCaffrey et al. (1995) found very high test-retest reliability of over .9 for an interval between 7 to 10 days. Appropriate normative data for this measure are available (Mitrushina, Boone, & D'Elia, 1999). Practice effects for this measure have been noted (Lezak et al., 2004).

Trail Making Test, Parts A & B

The Trail Making Test A and B (Army Individual Test Battery, 1944) is a two-part, timed, paper-and-pencil test. Part A measures speed for attention and concentration, visual search and motor function, as well as sequencing. Part B also measures attention and concentration but with more complex sequencing, as well as shifting sets and mental flexibility. Part A asks the participant to connect, via penciled lines, 25 ascending encircled numbers (1-25) randomly distributed on a single sheet of paper. Part B requires the participant to shift sets by consecutively connecting 25 numbers and letters in alternating order (1-A-2-B-3...L-23). Participants are encouraged to work as quickly as possible and are asked to correct any mistakes pointed out by the examiner. It takes about five minutes to complete this test. Scoring is identical for Parts A and B, and is based on completion time.

A principal components analysis showed that Part B was based on visual scanning, attention, and conceptual reasoning (O'Donnell, MacGregor, Dabrowski, Oestreicher, & Romero, 1994). Reliability coefficients for this measure are generally above .60 (Lezak et al., 2004). Appropriate normative data for this test are available (Spreen & Strauss, 1998).

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (Heaton, 1981) is a demanding task designed to assess problem-solving abilities over changing environmental conditions. It comprises four stimulus cards (one red triangle, two green stars, three yellow crosses, four blue circles), and two identical 64-card response decks, each containing simple geometric designs (circle, square, triangle, cross), color (red, green, blue, yellow), and number of designs per card (1, 2, 3, 4). The participant is instructed to match cards from the response deck to one of the

four stimulus cards according to a prescribed sorting rule (color, form, or number) based solely on limited feedback (correct/incorrect) from the examiner. Following every 10 consecutive cards correctly sorted, the examiner, unknowingly to the participant, changes the sorting rule. The test is terminated when the participant has completed either six sets of 10 correct placements or uses 64 cards without accurately obtaining a single sorting rule. Scoring consists of computing the total number of correct responses, as well as the number of perseverative responses.

The Wisconsin Card Sorting Test is appropriate for repeated administration (Tate, Perdices, & Magiotto, 1998). Following a test-retest interval of five months among a sample of 50 undergraduate students, few practice effects were reported (Ferland, Ramsay, Engeland, & O'Hara, 1998). Spreeen and Strauss (1998) concluded that the Wisconsin Card Sorting Test most likely consists of two factors, problem-solving and inability to maintain set. Appropriate normative data for this test are available (Heaton, Chelune, Talley, Kay, & Curtiss, 1993).

Language function

Boston Naming Test

The Boston Naming Test (Goodglass, Kaplan, & Weintraub, 1983) is a popular test designed to measure expressive language difficulties. It comprises 60 black ink drawings of objects, ranging from easy, high frequency words (e.g., comb) to uncommon words (e.g., abacus). Pictures are shown individually and the participant is asked to spontaneously name the object. If the picture is unnamed within 20 seconds or if it is misperceived, a description of the picture (stimulus cue) followed by a phonemic cue (initial sound of the picture) is provided. Administration typically begins at item 30 (harmonica). However, if

any of the next eight items are failed, items are administered in a backwards order starting at item 29 until eight consecutive items are passed and then the forward direction of object naming is resumed. The test is discontinued after six consecutive errors and usually takes about 10 to 15 minutes to complete. The score is computed by adding the total number of spontaneously correct items plus the number of items correctly named with the aid of a stimulus cue.

Concurrent validity for the Boston Naming Test has been supported using the Visual Naming Test of the Multilingual Aphasia Examination (Benton, Hamsher, & Sivan, 1994; Axelrod, Ricker, & Cherry, 1994). This measure also supports high internal consistency with a Cronbach's alpha of .95 (Franzen, Haut, Rankin, & Keefover, 1995) and test-retest reliability of .95 over an eight-month period (Sawrie, Chelune, Naugle, & Luders, 1996). Normative data for this instrument are available (Heaton, Avitable, Grant, & Matthews, 1999).

Controlled Oral Word Association Test

The Controlled Oral Word Association Test (Spreen & Benton, 1969) measures letter fluency and the ability to shift sets. The participant is asked to spontaneously produce words (excluding proper nouns) starting with the letter "F" for one-minute. The procedure is immediately repeated for the letters "A" and then "S," requiring the participant to shift sets. It takes about 5 minutes to administer this test. The total score is the number of admissible words for all three letters, excluding proper nouns, incorrect words, variations, and repetitions.

Johnstone, Holland, and Larimore (2000) concluded that factor analytic studies of the Controlled Oral Word Association Test loaded on several factors including verbal

knowledge, reading-writing, and abstract mental operations. Following an interval of 19 to 42 days, desRosiers and Kavanagh (1987) found test-retest reliability to be .88 among a sample of head-injured adults. Normative data for this instrument are available (Spreen & Strauss, 1998).

Motor function

Grooved Pegboard Test

The Grooved Pegboard Test (Reitan & Wolfson, 1985) is a brief measure of visual-motor dexterity that is sensitive to general slowing. It consists of a small metal board with 25 slotted holes, each angled towards a different direction. The participant is instructed to lift ridged, metal pegs from a storage container and rotate each peg into proper position for accurate insertion. Both hands are typically tested and scoring consists of the latency to correctly insert all 25 pegs per hand.

Among a sample of 56 healthy women, the test-retest reliabilities over a six-month period for the Grooved Pegboard were .76 and .78 for the dominant and non-dominant hands, respectively (Ruff & Parker, 1993). Appropriate adult normative data for the Grooved Pegboard Test are available (Heaton, Grant, & Mathews, 1991).

Processing speed

Digit-Symbol Coding and Symbol Search

The Processing Speed Index of the Wechsler Adult Intelligence Scale – Third edition (WAIS-III; Wechsler, 1997b) assesses the capacity to process visual information quickly. This index is composed of two subtests, Digit Symbol-Coding and Symbol

Search. Given that the psychometric properties of the WAIS-III are among the most highly regarded, each of these subtests will be only briefly reviewed.

Digit Symbol-Coding requires the participant to copy as many symbols that are paired with numbers as possible, in a 120-second time limit. The Symbol Search subtest is a new addition to the WAIS-III and comprises 60 items of paired groups of symbols. The participant is instructed to indicate whether the target symbol appears in the search group of symbols. There is also a time limit of 120-seconds. For each subtest, participants' receive one point per correct response.

The psychometric properties of the WAIS-III subtests are exceptional (Groth-Marnat, Gallagher, Hale & Kaplan, 2000). Average internal consistency for the Processing Speed Index as a whole, as well as for the individual subtests is excellent (Kaufman & Lichtenberger, 1999). Among women and men 55 to 74 years old, test-retest reliability over a period of 2 to 12 weeks for the Processing Speed Index, Digit Symbol-Coding, and Symbol Search was .90, .89 and .79, respectively (Wechsler, 1997b). Practice effects are generally considered to be mild in nature (Lezak et al., 2004). Extensive age-stratified normative data are also available in the manual that accompanies the test (Wechsler, 1997b, 1997b).

Trail Making Test, Part A

See Trail Making Test, Parts & B in "executive function" section.

Verbal learning and memory

California Verbal Learning Test - II

The California Verbal Learning Test - II (Delis et al., 2000) is a multi-component, verbal learning and memory test. It provides information regarding learning strategies (e.g., semantic and/or serial clustering) over repeated trials, types of errors (e.g., intrusions, perseverations), and vulnerability to interference. It also evaluates processes related to encoding, storage, retrieval, and recognition.

The participant is orally presented a list of 16 words from four semantic categories (furniture, vegetables, ways of traveling, animals) over five trials. At the end of each trial, the participant is asked to recall as many items, in any order, as possible. An interference trial of another 16 words is then presented and free recall for this list is also examined. Subsequently, the participant is asked to recall items from the first list to evaluate interference effects. A test of cued recall from the four semantic categories and a short delay free recall trial are also administered. Following a 20-minute delay, free recall, cued recall, and a recognition trial that includes 32 foils are given; the participant is not aware that further trials will be administered after the delay.

A factor analysis of the California Verbal Learning Test - II revealed high internal validity and is comparable to the factor solution of its predecessor (Delis et al., 2000), the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987). The authors reported six identifiable factors, accounting for 76% of the total variance: (i) General Verbal Learning (delayed recall and recognition), (ii) Response Discrimination (intrusion errors and recognition response bias), (iii) Primacy-Recency Effects, (iv) Organizational Strategies (semantic and serial clustering), (v) Recall Efficiency (repetition errors and subjective clustering), and (vi) Acquisition Rate. The split-half reliability among a clinical

sample was reported to be .96. Over a median interval of 21 days, test-retest reliability for Trials 1-5 was very good (.82). Normative data are available in the manual.

Logical Memory I and II subtest of the WMS-III

The Logical Memory I and II subtest of the WMS-III assesses both immediate and delayed memory for verbally presented conceptual information. For Logical Memory I, the participant listens to two brief stories and is asked for immediate recall. Unlike its predecessor, the Wechsler Memory Scale – Revised (Wechsler, 1987), the second story is read twice to gauge learning over two trials. The participant is asked to remember as much as she can about the stories because she will be asked about them again. After about a 30-minute delay, Logical Memory II is administered and the participant is asked to recall the stories. Scoring follows standard manual instructions and consists of allotting one point per story unit, with a maximum score of 25.

Test-retest reliability for Logical Memory I and II were .77 and .76, respectively (Wechsler, 1997a). The Logical Memory subtest has the highest association with other WMS-III subtests of verbal memory (e.g., Verbal Paired Associates I, $r = .48$) and the lowest correlations with nonverbal subtests (e.g., Faces I Recognition, $r = .14$), supporting both construct and discriminant validity. Normative data for the individual subtests of the WMS-III are available in the manual (Wechsler, 1997a).

Visual learning and memory

Rey Visual Design Learning Test

The Rey Visual Design Learning Test (Rey, 1968) is a measure of memory span, new visual learning, and recognition memory. The participant is presented with 15 simple geometric shapes, each on its own presentation card (10 x 7 cm), at a rate of two seconds

per card for five trials. After each trial, the participant is asked to draw as many of the designs as possible from memory. Following the last trial, the participant is also asked to pick out the 15 designs previously shown from a display of 30 designs containing 15 foils. Recall and recognition trials are re-administered after a 20-minute delay; the participant is not aware that further trials will be administered after the delay.

Compared to the selection of verbal memory tests (see Lezak, 2004 and Spreen & Strauss, 1998), there are fewer non-verbal memory tests available. Unlike other more popular non-verbal instruments of memory (e.g., Rey-Osterrieth Complex Figure (Osterrieth, 1944), the Rey Visual Design Learning Test has the added advantage of measuring learning over repeated trials. As such and despite limited psychometric data, the Rey Visual Design Learning Test is considered to be the best non-verbal equivalent to the California Verbal Learning Test. With regard to psychometric properties, test-retest reliability among healthy young adults was reported to be .45 over a one-month interval and appropriate normative data for this measure are available (Spreen & Strauss, 1991).

Family Pictures I and II subtest of the WMS-III

The Family Pictures I and II subtest is a new addition to the WMS-III and is considered to be the visual analog to Logical Memory I and II (Mitrushina et al., 1999). The participant is presented with four hypothetical family scenes, each presented for only 10 seconds. After all of the scenes have been viewed, the participant is asked to recall the characters, what they were doing, and where they were positioned. The participant is asked to remember as much as she can about the scenes because she will be asked about them later on. Following about a 30-minute delay, Family Pictures II is administered and the participant is once again asked to recall the details of each of the scenes. Scoring also

follows standard manual instructions and consists of allotting points according to accurate recall of the characters, their location, and particular activity.

Test-retest reliability for Family Pictures I and II were .66 and .71, respectively (Wechsler, 1997a). As mentioned, normative data for the individual subtests of the WMS-III are available in the manual (Wechsler, 1997a).

Visuospatial function

Block Design subtest of the WAIS-III

The Block Design subtest of the WAIS-III is a visuospatial constructional task requiring non-verbal reasoning ability and physical manipulation. The participant is presented with two, four, or nine red and white blocks and asked to duplicate a model provided by the examiner or replicas of pictures. Each test item has a maximum time limit of 30 to 120 seconds for precise reproduction. Scoring depends on both accuracy and speed.

As mentioned, the WAIS-III has some of the most highly respected psychometric properties in the field. Split-half reliability and test-retest reliability for the Block Design subtest were reported to be .86 and .82, respectively (Wechsler, 1997b).

Working memory

Working memory measures the ability to attend to information, hold it momentarily, manipulate it, and then provide a response (Lezak et al., 2004). The WAIS-III subtests of verbal working memory were selected and these consist of: (i) Arithmetic, (ii) Letter-Number Sequencing, and (iii) Digit Span. The Spatial Span subtest from the Wechsler Memory Scale – Third edition (WMS-III; Wechsler, 1997a) was employed as a nonverbal

measure of working memory. For each subtest, the task is made progressively more difficult by increasing the amount of information to be manipulated. Extensive age-stratified normative data are available in the manual (Wechsler, 1997a). Once again, given that the psychometric properties of the WAIS-III and the WMS-III are among the most highly regarded, each of these subtests is only briefly described.

Arithmetic

This subtest asks participants to compute arithmetic problems without the aid of pencil and paper. The test-retest reliability for arithmetic was found to be .86 (Wechsler, 1997b). The Arithmetic subtest demonstrates both construct and discriminant validity.

Digit Span

The Digit Span subtest consists of two parts, Digits Forward and Digits Backward. Participants are orally presented with an increasingly longer series of numbers and are required to repeat the sequence in either the same (Digits Forward) or reverse order (Digits Backward).

The test-retest reliability for Digit Span was found to be .83 (Wechsler, 1997b). This subtest has the highest association with other WMS-III subtests of working memory such as Letter-Number Sequencing ($r = .45$) and the lowest association with measures of processing speed (e.g., Digit-Symbol Coding, $r = .36$), showing both construct and discriminant validity.

Letter-Number Sequencing

The Letter-Number Sequencing subtest asks the participant to sequentially order a series of random numbers (1 to 9) and letters. For a correct response, the participant is required to remember the items, reorganize them, and then relay the numbers in ascending order and the letters in alphabetical order.

Test-retest reliability over a 2 to 12 week period for the Letter-Number Sequencing subtest was .74 (Wechsler, 1997a). This subtest has the highest correlations with other WMS-III measures of working memory such as Digit Span (.57) and the lowest association with subtests involving perceptual organization like Block Design (.44), supporting both construct and discriminant validity, respectively.

Spatial Span

The Spatial Span subtest is the visual analogue to the Digit Span subtest. Using a three-dimensional board, the participant is asked to duplicate a progressively longer visual-spatial sequence provided by the examiner in either the same (Spatial Span Forward) or the reverse sequence (Spatial Span Backward).

The test-retest reliability over 2 to 12 weeks for Spatial Span was reported to be .71 (Wechsler, 1997a). This subtest has the highest association with other WMS-III subtests of working memory (e.g., Letter-Number Sequencing, $r = .45$) and the lowest correlations with nonverbal subtests (e.g., Faces I Recognition, $r = .14$), once again, supporting both construct and discriminant validity.

Consonant Trigrams

The Consonant Trigrams test (Brown, 1958), also known as the Brown-Peterson procedure, is a classic measure of divided attention and information-processing capacity (Mitrushina, Boone, & D'Elia, 1999). The participant listens to a consonant trigram (CCC) and is asked to recall the three consonants after a delay of 0, 9, 18, or 36 seconds. During the latter three intervals, the participant is engaged in an interference task to prevent rehearsal done by counting backwards aloud by three's from different numbers (e.g., 100-97-94). Performance is expected to deteriorate with increases in delay. It takes about 10 minutes to complete this test and the score is based on the total number of correct responses.

The Consonant Trigrams test is a frequently used and widely accepted instrument in clinical neuropsychological settings as evidenced by their inclusion in two popular compendiums of clinical neuropsychological tests (Lezak et al., 2004; Spreen & Strauss, 1998). Appropriate normative data for this test are accessible (Stuss, Stethem, & Pelchat, 1988).

Measure of psychological functioning

Beck Depression Inventory-II

The Beck Depression Inventory-II (BDI-II) is a 21-item self-report questionnaire designed to measure the severity of depressive symptoms in adults and adolescents (Beck, Steer, & Brown, 1996). Items were developed to reflect the criteria for a diagnosis of depressive disorders as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth edition (American Psychiatric Association, 1994). This very popular inventory has demonstrated convergent and discriminant validity (Beck et al., 1996).

Internal consistency of the BDI-II is very high with coefficient alpha's in the .92 range (Beck et al., 1996). It takes about 10 minutes to complete this inventory, is easily scored, with scores ranging from 0 to 63.

Profile of Mood States

The Profile of Mood States (POMS) is a 65-item, self-report instrument designed to measure mood and affective states. Using adjectives or short phrases, the participant indicates her mood and feelings for the "past week including today," using a five point Likert scale, ranging from "Not at all" to "Extremely." It takes about five minutes to complete this inventory and scores range from 0 to a maximum of 60. This measure is a commonly used instrument in the evaluation of illness- and treatment-related adjustment to breast cancer (Brezden et al., 2000; Cimprich et al., 2005; Roscoe et al., 2002).

The validity of the POMS is well established (McNair et al., 1992). It supports considerable face validity and is highly correlated with other measures of mood states, suggesting good construct validity. Based on several independent factor analytic studies, this measure consists of six identifiable subscales: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. A Total Mood Disturbance score composed of the aforementioned factors can be employed as an indicator of global affective state.

The Profile of Mood States is suitable as a measure of change in mood over time (McNair et al., 1992). McNair et al. (1992) reported very high internal consistency for this inventory, in the .87 to .95 range. Moreover, among a sample of 47 breast cancer patients, the Depression-Dejection subscale had high internal consistency (.86 to .93; Cimprich & Ronis, 2001). For each of the subscales, test-retest reliability over a median of 20 days

(range = 3 – 100 days) was satisfactory: .70 (Tension-Anxiety), .74 (Depression-Dejection), .71 (Anger-Hostility), .65 (Vigor-Activity), .66 (Fatigue-Inertia), and .68 (Confusion-Bewilderment). Normative data are available in the manual (McNair et al., 1992).

APPENDIX F

DEMOGRAPHIC AND PAST MEDICAL HISTORY QUESTIONNAIRE

Chemotherapy Study

Demographic Information and Past Medical History

1. How old are you?
2. What is your marital status?

Work-Related Information

3. What is the highest level of education you have completed?
4. What is your current occupation?
5. If employed outside the home, how many hours per week do you work?
6. What level are you (if applicable)?
7. Do you supervise other people at work?
8. If yes, how many?
9. What is your current salary?
10. What was your highest level of employment?
11. During what period of time were you employed at that level?
12. What was your highest salary?
13. During what period of time did you receive that salary?
14. (If current level of employment not the highest) Why was there a decline in your level of employment?
15. (If current salary not the highest) Why was there a decline in your salary?
16. Do you do volunteer work?
17. If so, what kind of volunteer work do you do?

18. How many hours per week are you engaged in volunteer work?
19. Are you currently going to school?
 20. If yes, what program are you enrolled in?
 21. If yes, how many hours per week are you studying?
 22. What is your average grade at present?

Health-Related Information

1. Have you ever had any serious mental illness (such as depression, anxiety attacks, schizophrenia) that interfered with your ability to carry out your usual social or work activities, required hospitalization, or required treatment with drugs or other treatments (e.g., ECT)? If yes, provide details.
2. Have you ever had any form of neurological illness or injury (i.e., an illness that affects the brain or spinal cord, such as Parkinson's disease, multiple sclerosis, stroke, Alzheimer's disease or dementia, lupus, aneurysm, closed head injury or severe concussion)?
3. Have you ever lost consciousness for any reason? If so, provide details.
4. Do you currently drink alcohol? If so, how much?

5. At the time of your life when you were drinking most heavily, how much alcohol did you drink?
6. For how long?
7. Apart from your chemotherapy or hormone treatments, what other medications (prescription, non-prescription, or holistic) do you use? How long taking?
Indication? Dose?
8. Do you use recreational drugs? If so, what drugs do you use and how much?
9. Have you used recreational drugs in the past? If yes, what drugs did you use, how much, and for how long?
10. Have you ever been diagnosed with cancer (of any type) before?
 11. If yes, what kind of cancer did you have, when did you have it, and how was it treated?
12. Have you ever received chemotherapy before?
 13. If yes, what did you receive, when, and for what reason?
14. Have you ever taken Tamoxifen before?
15. If so, when and why?

16. Are you currently taking hormones?
17. If so, what are you taking?
18. Were you taking hormones prior to being diagnosed with breast cancer?
19. If so, what were you taking and for how long?
20. Have you had a hysterectomy?
21. If yes, when and why?
22. Have you had your ovaries removed?
23. If so, when and why?
24. When did you have your last menstrual period?
25. When did you have your second-last menstrual period?

APPENDIX G

MEDICAL RELEASE OF INFORMATION



The Ottawa Hospital | L'Hôpital d'Ottawa

- ☐ Civic Campus
☐ General Campus
☐ Riverside Campus

CONSENT TO THE DISCLOSURE, TRANSMITTAL OR EXAMINATION OF A CLINICAL RECORD

I authorize the Ottawa Hospital, campus to release/obtain records pertaining to:

Patient's Surname

Given name (Please print)

Date of birth

Sex: ☐ M ☐ F

Spouse's full name

Name at birth/Alias

INFORMATION TO BE RELEASED TO/FROM (for the purposes of):

DATE (S) OF TREATMENT OR DISCHARGE:

COMMENTS:

Signature of person giving consent

Date

Name of witness

Signature

Relationship to patient if unable to sign

Reason for inability to sign

Contact phone number(s)

NB Authorization is valid for 90 days from date of signing.

Français au verso.

ONLY ORIGINAL INK SIGNATURE IS ACCEPTABLE FOR RELEASE OF HEALTH CARE INFORMATION



The Ottawa Hospital | L'Hôpital d'Ottawa

- ☐ Campus Civic
☐ Campus Général
☐ Campus Riverside

CONSENTEMENT À LA DIVULGATION, À LA TRANSMISSION OU À L'EXAMEN D'UN DOSSIER MÉDICAL

J'autorise l'Hôpital d'Ottawa, campus

à communiquer/obtenir des documents concernant :

Nom du (de la) patient(e)

Prénom (Veuillez imprimer)

Date de naissance

Sexe: ☐ M ☐ F

Nom au complet du (de la) conjoint(e)

Nom à la naissance/Autres noms

RENSEIGNEMENTS À COMMUNIQUER À/DE (aux fins de):

DATE (S) DU TRAITEMENT OU DU CONGÉ :

REMARQUES :

Signature de la personne donnant le consentement

Date

Nom du témoin

Signature

Lien avec le(la) patient(e) incapable de signer

Raison pour laquelle le(la) patient(e)

Numéro(s) de tél. de la personne ressource

NB Autorisation valable pendant les 90 jours suivant la date de signature.

English on other side.

**SEULE LA SIGNATURE ORIGINALE À L'ENCRE EST ACCEPTABLE AUX FINS DE
COMMUNICATION DE RENSEIGNEMENTS D'ORDRE MÉDICAL**

APPENDIX H
MEDICAL CHART REVIEW

Chemotherapy study
Chart Review

Subject No.: _____ Initials: _____

Group: _____

Date: _____

Chart Info:

1. Diagnosis (grade, node+/-, no. nodes involved)
2. Surgery (procedure, date, duration, type of anesthetic, complications)
3. Chemotherapy regimen (drugs, doses, cycle, no. of cycles, start date)
4. Hormonal treatment (yes/no, type, dose, start date)
5. Other medications (names, doses, indications, duration)
6. Involvement in other studies/clinical trials?
7. Radiotherapy (yes/no, no. of treatments, start date)
8. Past medical history (especially previous history of cancer, chemotherapy, radiation)
9. Other

APPENDIX I

ORDER OF TEST/QUESTIONNAIRE ADMINISTRATION

1. Quick test
2. WMS-III
 - a. Logical memory I
 - b. Family Pictures I
 - c. Letter-Number-Sequencing
 - d. Spatial span
 - e. Digit span
3. Trails A and B
4. Controlled Oral Word Association Test
5. Grooved Pegboard
6. WMS-III (25-35 minute delay)
 - a. Logical memory II
 - b. Family Pictures II
7. California Verbal Learning Test – II
8. Rey Nonverbal Learning Test
9. WAIS
 - a. Digit-symbol coding
 - b. Block design
 - c. Arithmetic
 - d. Symbol search
10. Rey Nonverbal Learning Test (delay)
11. Wisconsin Card Sorting Test
12. Consonant trigrams
13. Boston Naming Test
14. Profile of Mood States
15. Beck Depression Inventory - II