At the first International Cognitive Workshop in 2003, participants concluded that in order to determine more definitively the impact that cancer chemotherapy has on cognitive function, there needed to be an increase in the number of prospective, longitudinal studies examining the subject. Since that first workshop, the field has seen a relative increase in the number of these studies with general conclusions being mixed. While some studies report declines in cognitive function following administration of chemotherapy, others have found no significant change in cognitive function. And while some meta-analyses have found evidence suggesting that there are indeed cognitive changes associated with cancer therapy, many of the studies under review have not been without flaw, and the methodological issues associated with these studies have been discussed previously (1).

One area of cancer research that has seen a rapidly escalating amount of attention over the last few years has been breast cancer. As the ability to clinically detect and subsequently treat breast cancer has advanced over time, there has been a concomitant increase in survivorship. Women are now living for longer periods of time following the diagnosis of breast cancer, with 5 and 10 year relative survival rates for all stages approaching 90% and 80% respectively (2). Yet, as survivors live to older ages, the long-term effects that cancer therapy such as chemotherapy and hormonal therapy have on quality of life and ability to function, both mentally and physically, must be called into question. Breast cancer survivors commonly complain about having problems...
maintaining their attention and concentration while performing activities of daily life. Additionally, many report having problems with their memory and with concentration (3). Taken together, these issues constitute amongst patient circles what is known as *chemo brain*.

As noted previously, the methodological inconsistencies across studies of cognitive function in breast cancer patients has made it increasingly difficult to draw inferences from findings amongst various studies. To this end, Vardy et al. have made recommendations for future research efforts that attempt to reduce, if not completely remove, some of these difficulties by discussing ways in which to standardize methods (1, 4). Yet, while much attention has been given to this area, little attention has been paid to the actual results of studies concerning cancer, cancer therapy, and their effects on cognition and what those results attempt to tell us, irrespective of the methods employed. In light of this and in response to the constantly expanding research in this area, a need for a review of recently published results on the effects of cancer therapy on cognitive function is called for.

Here we review recent publications that have attempted to evaluate the effects of adjuvant hormonal therapy and chemotherapy on cognitive function in women diagnosed with breast cancer. Due to the vast number of publications in this area within the previous decade and the presence of existing meta-analyses of research as recent as 2005 (5), this review was limited to those studies published within the last three years. Additionally, to further narrow the field of review, we restricted the search strategy to include only studies focused on cognitive functioning in women receiving adjuvant therapy for breast cancer. A literature search was performed on PubMed, and only
studies which included the following keywords in their titles were selected: breast cancer and cognition or cognitive (dys)function or adjuvant chemotherapy or hormonal therapy. The reference list of each of the relevant studies that were selected were also searched to identify any other studies that may have met the above criteria, but which were not found within the literature search.

Ultimately, 22 published studies met criteria for inclusion in this review. Of these, fifteen [6-20](68.1%) aimed to examine the effects of adjuvant systemic therapy, i.e. chemotherapy or hormone therapy, on cognitive functioning in breast cancer patients through the utilization of neuropsychologic testing. Two of these examined cognitive function before the administration of chemotherapy or hormonal therapy, three looked at the level of cognitive decline following administration of hormonal therapy, and the remaining ten analyzed the effect of adjuvant chemotherapy on cognitive functioning. Of the remaining seven, three [21-23] (13.6%) were imaging studies, one [24](4.5%) was an electrophysiologic study, two [3,25](9.0%) focused on self-reporting of cognitive problems in women receiving adjuvant therapy for breast cancer, and one [26](4.5%) examined the methodological problems inherent in research in this area and suggested ways in which to conquer these issues.

When trying to determine the specific areas of cognitive function that may or may not be impaired by adjuvant therapy, one limitation of many studies is the selection of neuropsychological (NP) tests that investigators choose to employ. While a comprehensive battery including a large number of parameters may be the ideal option, there is currently no standardized battery, and researchers differ in opinion as to what should be included. Additionally, the utilization of such a large battery may not be
feasible in its administration without causing fatigue in the patient. Amongst the fifteen studies included here that used NP tests, the range of these tests and the number of cognitive domains they cover varies widely, with anywhere from 12-18 tests and 3-8 cognitive domains respectively. Early studies investigating the effects of adjuvant chemotherapy on cognitive function in women with breast cancer concluded that chemotherapy treated patients performed more poorly on NP parameters than control subjects [27, 28, 29]. However, the studies that have been carried out over the past three years have tended to show that if a deficit in cognition is produced, it is not only subtle, but also appears to peak directly after the course of treatment and then improve over time [11, 13, 20]. Others still have found no support of cognitive side effects from treatment [12]. However, the subtlety of these results may not be due to the lack of significant cognitive decline, but rather to a lack of sensitivity of NP measures to pick up on differences over time. Thus, the changes in memory and concentration that are often reported by breast cancer patients, no matter how subtle they may seem to appear, should by no means be considered clinically insignificant.

With factors such as the selection of cognitive domains and neuropsychological tests, appropriate study design, analysis at an individual and/or group level, and the choice of reference groups differing from study to study, it is of little surprise that the discovery of statistically significant differences in cognitive function in these women lack consistency across studies. In their study on cognitive functioning in breast cancer patients prior to adjuvant therapy, Ahles et al discovered that visual memory was one of the most common domains to contribute to their definition of ‘lower than expected cognitive performance’ [6]. Conversely, studies done by Collins et al. and Bender et al.
suggest that visual memory is impaired in breast cancer patients following the administration of chemotherapy and hormonal therapy, respectively [10,11]. Besides visual memory, the domains of working memory and verbal memory were also found to be impaired in multiple studies, both before the administration of adjuvant therapy [6] and after chemotherapy [11,14,16] and hormonal therapy [10,11]. In addition to memory specific domains, verbal fluency [6,9,13], attention [14,15], and overall cognitive function [8,19] were found to be impaired across multiple studies. However, the domains of cognitive function that were most often impacted across the fifteen studies included processing speed and executive function.

In two separate studies examining the cognitive effects of hormonal therapy in postmenopausal women suffering from breast cancer [8,9], both found processing speed to be one of the cognitive domains most affected following treatment. Of additional interest is that despite the fact that raw test scores for hormonal groups and healthy controls both fell within the normal range relative to published norms, Collins et al. found that women treated with anastrazole showed a 9-fold increase in risk of cognitive decline compared to healthy controls [8], suggesting that aromatase inhibitors may have a greater impact on cognitive functioning than selective estrogen receptor modulators (SERMs) such as tamoxifen. Lending further credence to the notion that processing speed is a commonly affected cognitive domain in women treated for breast cancer with adjuvant therapy, Reid-Arndt et al. found that a small percentage of women having undergone NP testing 6 and 12 months post-chemotherapy to evidence deficits in processing speed at each time point [13]. Additionally, Mehlsen et al. carried out a prospective study designed to look at whether cancer patients receiving chemotherapy experience cognitive
decline during treatment. Comparing the results of women with breast cancer who received chemotherapy and had undergone testing before chemotherapy and 6 months afterwards to a group of healthy controls as well as a control group of cardiac patients, no indications of cognitive side effects were found. However, a significantly higher proportion of healthy controls improved on a measure of processing speed compared to cancer patients [12], suggesting that some women receiving chemotherapy for their breast cancer continue to struggle with this cognitive domain after treatment.

Whereas the evidence against processing speed seems to be rather succinct, executive functioning appears to be less certain. In their study on the cognitive effects in post-menopausal breast cancer patients one year after treatment with chemotherapy, Collins et al. found no effect on executive functioning at 6 months following treatment, but a significant decline in executive function 18 months after treatment [11], despite finding that overall cognitive performance resolved within one year. Similarly, while finding that cognitive function remained stable for most patients during chemotherapy and that there was significant improvement in six of twelve cognitive tests over time, Hermelink et al. also found significant deterioration in a test of executive functioning approximately 5 months after the initiation of chemotherapy [20]. Conversely, Hermelink et al. found a favorable effect of chemotherapy-induced menopause on a test of executive function in breast cancer patients at the group level one year after baseline testing [18], and Jansen et al. found that mean executive function actually improved over time following the administration of four cycles of chemotherapy [19].
In addition to studies examining neuropsychological functioning in breast cancer patients given adjuvant treatment, other studies have strengthened the evidence for at least subtle, yet nonetheless important cognitive decline in these patients. Kreukels et al. attempted to define the neurophysiologic basis for cognitive problems subjectively expressed and objectively shown in the breast cancer patient population using a series of EEG studies. When breast cancer patients receiving different kinds of chemotherapy treatment were compared to breast cancer patients not treated with chemotherapy on an auditory oddball task, it was found that those treated with chemotherapy exhibited lower P3 amplitudes than those not treated with chemotherapy. Additionally, differences were found between chemotherapy regimens in regards to P3 latency. As authors note, this suggests that fewer neurons are firing synchronously in patients treated with chemotherapy [24].

Over the past few years, the use of imaging studies in attempts to determine specific areas of the brain impacted by administration of chemotherapy have been gaining popularity. In an MRI study exploring regional brain volume differences between breast cancer survivors given chemotherapy to those who had not been given chemotherapy, Inagaki et al. found that patients who were exposed to chemotherapy had smaller right prefrontal, parahippocampal, and cingulate gyri and precuneus at a mean of 4 months compared to those not exposed to chemotherapy. However, this distribution of regional volume difference was not found at a mean of 4.2 years after completion of adjuvant chemotherapy, suggesting that differences may recover over time [23]. In a structural and functional MRI study of monozygotic twins discordant for breast cancer, Ferguson et al. found that while the twin who contracted breast cancer and underwent chemotherapy
reported significantly higher levels of cognitive complaints than the healthy twin, they both performed similarly on NP testing. However, fMRI results revealed that compared to the healthy twin, across tasks associated with working memory the twin with breast cancer showed a wider level of spatial activation [22]. This recruitment of additional cortical area may be one reason contributing to the fact that cognitive dysfunction in these patients is only subtle. Finally, in a recent PET study carried out by Silverman et al, abnormal activation of the inferior frontal cortex was found during a short term memory task in chemotherapy treated breast cancer patients 5-10 years following treatment; while patients not treated with chemotherapy exhibited greatest activation in parietal and occipital cortices [21]. This apparent recruitment of additional frontal cortex corroborates with the findings of Inagaki et al. and suggests a mechanism by which cognitive decline remains subtle in this patients. In addition to abnormal cortical recruitment, it was also found that patients who had received hormone therapy exhibited significantly decreased basal ganglia activity compared to those who had not been given hormone therapy following chemotherapy.

Overall, it is evident that results of studies concerned with cognitive functioning in breast cancer patients following adjuvant therapy report a myriad of difficulties. While the methodological inconsistencies make it hard to draw inferences from study to study [26], it is clear that some cognitive domains appear to be more evidently impacted than others (executive function, processing speed, verbal memory), and thus should definitely be included when trying to determine the extent of cognitive decline. Despite studies analyzing group mean differences in cognitive function often reporting that no significant difference exists, the use of SRB or RCI analyses to investigate cognitive change at the
individual level can reveal subtle impairment that may have been obscured otherwise [14,16]. Also, the variation of the definition of cognitive impairment in these studies can have a large impact on the number of individuals classified as impaired. In a study conducted to look specifically at the issue of different definitions and reference groups on the impact of impairment, Schilder et al. found that the prevalence of cognitive impairment varied greatly depending on the strictness of the definition, with results ranging anywhere from 13.7 to 45.4% based on study specific controls and 1 to 36.6% based on published norms [7]. Finally, it is important to understand that while many studies provide support for the oft-noted lack of correlation between subjective complaints and objective evidence for decline {14,17,20], this should not render significant findings of cognitive deficit in these patients as inconsequential. The link between neuropsychological studies and imaging studies around cognitive function in breast cancer survivors provides strong evidence for impairment, and results of these studies should be used to help aid in the identification of the mechanism contributing to cognitive decline in breast cancer survivors.
Reference:


7.) Schilder CM, Seynaeve C, Linn SC. The impact of different definitions and reference groups on the prevalence of cognitive impairment: a study in postmenopausal breast cancer patients before the start of adjuvant systemic therapy. Psycho-Oncology 2009.


