**TITLE**

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**ABSTRACT**

**INTRODUCTION**

There are now over 3 million breast cancer survivors in the US [[1](#_ENREF_1)]. In 2015, approximately 240,000 new cases of invasive breast cancer are expected to be diagnosed in U.S. [[2](#_ENREF_2)]. In 1999 to 2005, the probability of dying from localized breast in the five years after diagnosis for women (ages 66-74) without comorbidities was 3% while dying from other causes was 5.1% [[3](#_ENREF_3)].

A substantial proportion of the improvement in mortality for early stage breast cancer (ESBC) has been attributed to breast cancer treatment [[4](#_ENREF_4)]. Primary treatment with surgery and radiation is often followed by adjuvant hormonal therapy or chemotherapy. In 2011, approximately 37% of all patients diagnosed with stage I-II breast cancer received adjuvant chemotherapy [[5](#_ENREF_5)]. Adjuvant chemotherapy is associated with modest effect on disease-free survival and overall survival and remains standard of care for selected women with ESBC. Using a pooled analysis of 60 randomized clinical trials, Early Breast Cancer Trialists' Collaborative Group reported an absolute improvement in 15-year overall survival with chemotherapy as 5-9% for women less than 50 years of age at diagnosis and 3% for ages 50-69 years at diagnosis [[6](#_ENREF_6)]. Chemotherapy, however, is associated with substantial short-term toxicity and risk of long-term adverse effects. Cognitive impairment has been reported as one of these long-term sequelae [[7](#_ENREF_7)].

Randomized trials of adjuvant chemotherapy have predominantly focused on evaluating effects on cancer recurrence and on treatment-associated short-term adverse effects. Less attention has been given to long-term adverse effects of these cytotoxic drugs, which may have significant negative impacts on health and QOL for breast cancer survivors long after their treatment ends.

The short-term cognitive dysfunction during chemotherapy measured by neuropsychological or neuroimaging assessments or self-report, also known as “chemo brain” or “chemo-fog,” is widely reported [[8](#_ENREF_8), [9](#_ENREF_9)]. Most studies in the current literature report a range of 15-50% incidence of short-term cognitive impairment in all treated patients [[10](#_ENREF_10)].

The causal mechanisms for the observed cognitive impairment following cancer treatment are still unknown. In previous reviews, Ahles et al and Mandelblatt et al [[9](#_ENREF_9), [11](#_ENREF_11)] have suggested risk factors that are consistent with theories of aging and provided following possible explanations breast cancer treatment-associated cognitive impairment:

1. The biology of cancer (e.g. inflammatory response triggering neurotoxic cytokines) may contribute to lower than expected cognitive performance.
2. Common risk factors for the development of both breast cancer and mild cognitive changes over years may exist; for example, poor DNA repair mechanisms and oxidative damage have been linked to risk of cancer and neurodegenerative disorders.
3. Certain hormonal therapies have been implicated in cognitive impairment after treatment for breast cancer. However, effects are not universal and may not be observed with all hormonal therapies. For instance, cognitive declines in verbal memory and executive function have been reported among women treated with tamoxifen (its target is also found in the frontal lobe and hippocampus) but not with aromatase inhibitors. Hormonal therapies may also be associated with increased DNA damage.
4. Genetic factors such as apolipoprotein E (*ApoE*) and catechol-O-methyltransferase (*COMT*) have been associated with age-related cognitive decline. For example, Ahles et al reported that breast cancer survivors who received chemotherapy and were ApoE ε4 –positive had greater impairment in the visual-spatial and visual memory domains compared with ε4-negative survivors receiving this same treatment [[12](#_ENREF_12)]. Also Small et al found that the patients with breast cancer treated with chemotherapy, who were COMT-valine carriers, performed worse on measures of attention compared with COMT-methionine homozygotes.
5. Treatment-associated (chemotherapy and radiation) increases in pro-inflammatory cytokines and reactive oxygen species that cross the blood brain barrier and activate microglia in the brain inducing local inflammation.

Knowledge about the long-term cognitive outcomes of chemotherapy for breast cancer would help clinicians and patients to weigh the potential harms versus benefits of adjuvant chemotherapy when making treatment decisions. Despite the convincing evidence of an association between cognitive impairment and chemotherapy in cross-sectional studies, the longitudinal cohort studies suggest a trend towards gain of lost function [[8](#_ENREF_8), [10](#_ENREF_10)]; hence, whether the cognitive function remains affected long after the completion of therapy is not clear.

To provide a more robust interpretation of the evidence, several meta-analyses of individual studies have been conducted [[8](#_ENREF_8), [13-15](#_ENREF_13)]. Methodological challenges in conducting a study evaluating cognitive impairment result in small sample sizes and fewer number of prospective studies available to be included in meta-analyses. Consequently, existing meta-analyses include studies that differ widely in terms of timing and types of neuropsychological assessments employed, definitions of cognitive impairment, and treatment regimens. The recent increase in number of good quality prospective studies investigating this issue makes it possible to select studies with comparable neuropsychological tests, timing of assessments and contemporary chemotherapy regimens without compromising the study power. In this study, we aimed to include the studies using contemporary regimens, including anthracyclines, taxanes, and cyclophosphamide- containing regimens with a one year or longer follow-up after baseline cognitive function assessed by validated and comparable neuropsychological tests. Our analysis included current studies investigating cognitive impairment following adjuvant chemotherapy for ESBC, which previous meta-analyses did not include.

Additionally, we aimed to address the lack of standard in assessment of cognitive function in women diagnosed with ESBC and treated with adjuvant chemotherapy. The current standard for assessment of cognitive impairment is neuropsychological testing. A wide range of tests is available to assess various domains of cognitive function, but many of these tests are not designed to detect subtle changes in cognitive function. Currently, there is no consensus for which neuropsychological tests are optimal to detect chemotherapy induced cognitive impairments. Use of various neuropsychological tests in different studies makes it difficult to compare them or pool assessment data during meta-analyses. We evaluated the sensitivity of domain specific neuropsychological tests to assess the changes in cognitive function in this setting.

**METHODS**

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for conducting this study.

**Inclusion Criteria**

Included studies satisfied all of the following criteria:

1. Investigating cognitive impairment in women of all ages with ESBC (stages I to IIIA) who received a contemporary adjuvant chemotherapy regimen, including anthracyclines, cyclophosphamide, or taxanes, used alone or in combination with endocrine therapies
2. Prospective cohort study design
3. Patients were assessed using at least one validated neuropsychological test of cognitive function
4. Baseline neuropsychological evaluation preceded chemotherapy initiation
5. Final assessment conducted one year or more after the baseline evaluation
6. Study data were adequate to calculate effect sizes for each neuropsychological test

**Exclusion Criteria**

Studies of women treated exclusively with regimens no longer recommended, such as CMF, or any non-standard chemotherapy regimen, were excluded.

**Search strategy**

MEDLINE, PubMed, Embase, and the Cochrane Library were searched for relevant English-language studies published between January 1990 and November 2015. The keywords used to search the databases included: *breast cancer, breast neoplasms, adjuvant chemotherapy, cognition disorders, neuropsychological tests, cognitive impairment, and cognitive* decline. We supplemented our searches with reference lists from other relevant systematic reviews and retrieved articles. Citations were managed using EndNote X7.

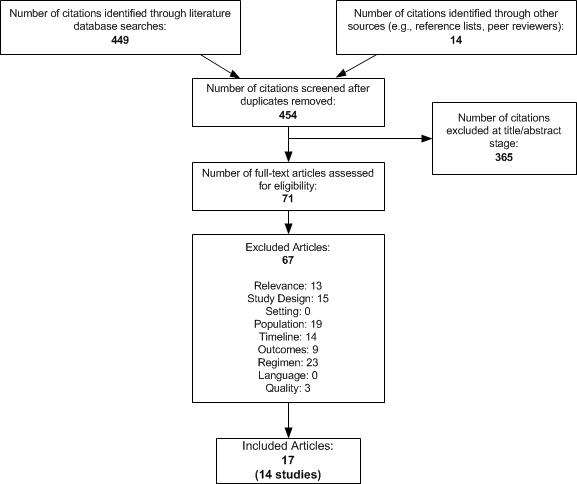


Figure 1: Flow Diagram: literature search and study selection ***(NEEDS UPDATED FIGURE)***

**Study selection and Data abstraction**

Two investigators independently reviewed abstracts and full-text articles against the priori-specified inclusion criteria noted above. Studies selected for full-text review were critically appraised by two investigators. [Insert statement re: quality assessment]. Data from the fair- or good-quality randomized controlled trials or observational studies was independently abstracted and reviewed for accuracy by two investigators. Discrepancies in both quality assessment and data extraction were resolved by consensus.

Neuropsychological test data were abstracted from each study. Four included studies [[16-19](#_ENREF_16)] did not provide sufficient data to calculate effect sizes; hence, their authors were contacted to request additional data on test results. All authors responded; one could not provide requested data because the study was conducted more than 10 years ago. In addition the author of a previous meta-analysis [[8](#_ENREF_8)] provided study group means and standard deviations at pre and post treatment time points for each cognitive test used in the source studies.

Neuropsychological Measures: insert why we grouped in such way – rational, ref etc.

Table 3: Cognitive domains assigned to neuropsychological measures

Sample size, mean test scores and standard deviation were abstracted for calculation of effect sizes. Also abstracted were patient characteristics: age, IQ, education, and measures of mood/anxiety/depression/fatigue; as well as study characteristics; time between assessments; and type of comparison group (no breast cancer versus breast cancer without chemotherapy versus endocrine treatment).

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**Statistical Analyses - *BEN***

Standardized mean differences (SMD) between pre-treatment and 12+ month post-treatment cognitive impairment measures is modeled with a multilevel mixed effects model. Cognitive domain is modeled as a fixed effect, with one effect size for each of the 8 domains. In our meta-analysis, we have multiple SMDs from each study (one for each cognitive test reported). Instead of modeling the random effect as a single parameter (as we would if we only had one observed SMD per study), we partition the random effect into variance components for observed SMD *i* and for study. The two variance components allow for the computation of an intraclass correlation.[[20](#_ENREF_20)] In addition, study-level mean age is included as a covariate. Age is centered around a mean of 50.9. Mathematically, the model is represented as

A second model to estimate a global SMD is

Models were estimated using the rma.mv() function from the metafor package for R 3.2.2. Full details of the analysis can be found at https://github.com/benjamin-chan/AEAfterBreastCaACT#cognitive-impairment.

**14. Risk of bias in individual studies** Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis

**15. Data Synthesis**

**a.** Describe criteria under which study data will be quantitatively synthesized

**b.** If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I2, Kendall’s tau)

**c.** Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)

**d.** If quantitative synthesis is not appropriate, describe the type of summary planned

* + Meta-regression - Do we have enough power to look into any of the moderators?

Outcomes by domain were considered to allow comparisons of effect sizes by study and to report summary mean effect size. The within and across study effect sizes of individual tests were examined and commonly used individual measures with larger effect sizes were identified. We also examined whether common individual measures based on neuropsychological tests represented cognitive domains with a purpose of recommending the use of specific tests in future studies to reduce the redundant testing.

**16. Meta-bias(es)** Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)

A funnel plot was used to assess the possibility of publication bias. [reference: Sterne JAC, BMJ 2011;343:d4002, <http://www.bmj.com/content/343/bmj.d4002>].

**RESULTS**

**Table 1.** Summary of meta-analyses included longitudinal cohort studies

**Table 2.** Neuropsychological measures assigned to specific cognitive domains by the included studies

**Table 3.** Assignment of neuropsychological measures to specific cognitive domains for the analysis

**Table 4.** Characteristics of participants in included studies

**Table 5.** Weighted mean effect sizes for each study (both fixed and random effects?)

**Table 6.** Weighted mean effect sizes of neuropsychological tests and heterogeneity for each cognitive domain

**Figure 2:** Forest plot of cognitive domain weighted effect sizes

**Table 7.** Meta-analytic regression results for moderator variables

**Figure 3:** Publication bias

**DISCUSSION**

* Ono paper investigated many of the questions I was interested:
  + Compared cross sectional vs cohort
    - Included cohort studies as cross sectional
    - Reported effect sizes by study and by domain
    - Discussed deficit vs decline – problems with defining deficit
  + They conducted a meta-regression to investigate the effect of time-since treatment, which was significant for cross sectional studies; we already stratified on study design and can investigate both short and long-term cognitive outcome
  + Did they look at the comparison: chemo vs control or just difference from baseline to next assessment?
  + Some of the moderators in Ono’s paper and in others are not relevant here: study design and chemo regimen
* In cross sectional:
  + Attention, executive function, motor function, processing speed and short-term memory were significantly worse in chemo compared with controls.
* In prospective:
  + No post-chemo decline among brca patients, but improvement instead.This suggests recovery and practice effects, but there may be some sub-groups (like older patients-see Ahles JCO study) who do not improve.
  + Cognitive domains (except visuospatial) that showed less impairment in cross sectional studies more likely to show greater improvement in prospective
* Methodological issues to discuss:
  + need for larger sample sizes to detect the difference between cognitive decline due to normal aging process vs chemo-related
  + better study designs for comparison – comparison group of normal individuals vs no chemo
  + long-term quality data is still missing. It would be important to follow these patients for the effect of chemo on regular aging association cognitive problems.
  + differences in patient populations
    - age
    - education
    - genetics such as vulnerable alleles of genes like *APOE* and *COMT*
    - cognitive reserve
    - endocrine and radiation tx
    - pre-existing psychiatric issues, most studies either screen out those with active psychiatric disorders or do not examine psychiatric symptoms in analyses.
  + NP test associated –
    - discuss NIH Toolbox and other efforts http://www.nihtoolbox.org/WhatAndWhy/Cognition/Pages/default.aspx
    - variability of instruments used
    - domain assignment
    - criteria for defining change
    - practice effects
    - sensitivity of the NP assessments to detect small changes
  + timing of baseline assessment – ideally before diagnosis
    - mood-related issues, surgery (effect of anesthesia)
    - there is increased risk for symptom of depression and anxiety after cancer diagnosis [[21](#_ENREF_21)]. While some have failed to find a relationship between mood symptoms and cognition prior to chemotherapy [[22](#_ENREF_22)], there is recent evidence that symptoms of trauma stemming for cancer diagnosis may mediate aspects cognitive functioning [[23](#_ENREF_23)]. The direct and contextual effects of mood and adjustment issues on cognitive functioning requires extensive further study.

Recommendations:

* If we aim to provide recommendation for what tests to be used to assess cognitive domains, maybe we can investigate combining frequently used tests and comparing effect sizes with other tests. Not hypothesis testing but exploring whether the results vary.
* Reporting of neuropsychological test results in individual studies – perhaps providing raw scores to aid
  + future meta-analyses eliminating time consuming requests from original authors
  + reproducibility of the results
* Can we identify subgroup of women who might be at higher risk? Or can we make any suggestions?
  + Discuss age-related phase-shift hypothesis Fig 2 from Ahles paper [[11](#_ENREF_11)]

**Existing meta-analyses**

Majority of the current literature evaluating cognitive impairment after chemotherapy for breast cancer consists of cross-sectional studies with less than one-year follow-up. These studies showed a small to moderate impact of chemotherapy on cognition in the short-run when women who received chemotherapy are compared to women who have not had chemotherapy. In some instances, the magnitude of effect size depended on study design and the affected domains varied study to study. Included studies were heterogeneous with respect to comparison group, chemotherapy regimens and neuropsychological tests. Short-term prospective studies (mostly few weeks – 6 months) showed improvement over time in chemotherapy group when compared to individuals’ own baseline measures. Table 1 provides a summary of current meta-analyses with some long-term follow-up data.

Meta-analysis by Falleti et al [[13](#_ENREF_13)] was the first study that included longitudinal data with baseline assessment. It included five cross-sectional and one prospective studies with a one year follow-up. The analysis of cross-sectional studies showed small to moderate effect sizes of the cognitive domains assessed with chemotherapy group performing worse than control and small to large effect sizes for prospective study with an improvement in cognitive function over time. Age, time since last chemo and percentage of patients currently taking tamoxifen were moderators of effect sizes in cross-sectional studies and the study type affected the magnitude of effect. Stewart et al [[14](#_ENREF_14)] built on Falleti meta-analysis by including another cross-sectional study. It replicated Falleti study results with small to medium cumulative effect sizes of cognitive impairment for chemotherapy group compared to control. The effect of study design or any potential moderators were not evaluated.

Third meta-analysis, Jim et. al. [[15](#_ENREF_15)], included nine cross-sectional and eight propective studies of 807 patients treated with chemotherapy. Comparisons of breast cancer patients who received chemotherapy to local therapies, non-breast cancer control or their own baseline were conducted for eight cognitive domains: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability. Chemotherapy group performed worse than non-cancer controls in verbal ability and worse than no chemo in visuospatial ability with small effect sizes. No signtificant moderator effect was found.

Meta-analysis by Ono M et. al. [[8](#_ENREF_8)] is the most current and comprehensive one to the date. This meta-analysis aimed to identify the magnitude of cognitive impairment and factors that moderate the magnitude of impairment among breast cancer patients treated with adjuvant chemotherapy. The study included total of 27 studies with 1562 breast cancer patients, who received a wide range of chemotherapies, and 2799 control individuals. A total of 737 individual effect sizes were calculated for eight cognitive domains: attention, executive function, long-term memory, short-term memory, speed of processing, language, visuospatial and motor function. Fixed and and random effects models were used to calculate weighted mean effect sizes for cross-sectional (varied from -1.12 to 0.62) and longitudinal studies (varied from -0.29 to 1.12). Each cognitive domain produced small effect sizes for cross-sectional and prospective longitudinal studies (ranging from -0.25 to 0.41). For cross-sectional studies, significant association between adjuvant chemotherapy and cognitive impairment that held across studies with varied methodological approaches. Attention, executive function, motor function, processing speed and short-term memory were significantly worse in chemotherapy group compared with controls. For prospective studies, cognitive functioning improved over time after chemotherapy completed. Cognitive domains (except visuospatial) that showed less impairment in cross-sectional studies showed greater improvement in prospective studies. Greater cognitive impairment was reported in cross-sectional studies comparing chemotherapy group with healthy controls. Cognitive impairment was present among breast cancer patients irrespective of a history of chemotherapy. Meta-analytic regression using a random effects model was employed to investigate the moderator effect of time since chemotherapy, average age and comparison group type. For cross-sectional studies, significant moderator effect of control group and education was found. For prospective studies, moderator variables together did not explain the variability in effect sizes, but older age at treatment was associated with poorer performance.

Jansen CE et al. [[24](#_ENREF_24)] and Vardy J et al. [[25](#_ENREF_25)] have also conducted meta analyses investigating cognitive impairment after chemotherapy; however, their investigations included not only early stage breast cancer, but all stages of various malignancies. Both found the patients receiving chemotherapy had lower neuropsychological test scores compared to patients who did not receive chemotherapy or normative data. However, these effects were either not significant or small to moderate.

Existing evidence seems to support a small to moderate cognitive decline during adjuvant chemotherapy and a recovery shortly after chemotherapy ends. However, there is still no convincing evidence whether this improvement remains in place or a later effect emerges as these women age.

**Sensitivity of neuropsychological tests**

Only one study, Jansen et. al. [[26](#_ENREF_26)] so far attempted to identify the sensitivity of neuropsychological tests to detect the impairment in a specific domain in this setting using a combination of 13 cross-sectional and prospective studies. The authors calculated and ranked the weighted standardized mean difference effect sizes for each test indicating the direction and magnitude of difference between women with breast cancer treated with chemotherapy and a control group. Each cognitive domain included two to six neuropsychological tests. The following tests demonstrated the most notable performance decrements in each cognitive domain: Attention/concentration – Wechsler adult intelligence scale (WAIS) digit span backward (ES= -0.448912); Executive function – Booklet category test (ES= 0.456752); Information processing speed – Paced auditory serial addition test (ES= -0.538267); Language – High sensitivity cognitive scale (HSCS) language subset (ES= -0.434461); Motor function – Grooved pegboard (ES= -0.955051); Visuaospatial skill – WAIS block subtest (ES= -554656); Verbal memory – HSCS memory subset (ES= -0.453015); Visual memory – Rey-Osterrieth complex figure test delayed recall (ES= -0.373973)

The Jansen meta-analysis has several limitations. It did not investigate changes from baseline, but the difference between the cases and a control group, the study population was heterogeneous in terms of chemotherapy regimens used and time of assessment since treatment. They also included studies that used HSCS to assess cognitive function. ***KATHLEEN – how can we explain why this test is not a good measure for this setting?*** Hence, confirmation of the Jansen results and an investigation of this question in prospective studies are still lacking.

Identifying the optimal neuropsychological tests to detect cognitive changes in women with breast cancer who are treated with chemotherapy, and consistently using them in future assessments would be a valuable contribution to the field especially for future meta-analyses.

**CONCLUSION**

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**Table 1.** Summary of meta-analyses included longitudinal cohort studies

|  |  |  |  |
| --- | --- | --- | --- |
| Author (Year) | Characteristics | Results | Conclusion |
| Falleti (2005)  [[13](#_ENREF_13)] | K= 6  5 cross sectional  1 prospective | For the cross-sectional studies, each of the cognitive domains assessed (besides attention) showed small to moderate effect sizes (-0.18 to -0.51).  The effect sizes for each study were small to moderate (-0.07 to -0.50) and regression analysis detected a significant negative logarithmic relationship between study effect size and the time since last receiving chemotherapy.  For the prospective study, effect sizes ranged from small to large (d= 0.11-1.09) and indicated improvements in cognitive function from T0 to T1 and T2. | Cognitive impairment occurs reliably in chemotherapy, but that the magnitude of this impairment depends on the type of design that was used (i.e. cross-sectional or prospective). |
| Stewart (2006)  [[14](#_ENREF_14)] | K= 7  6 cross sectional  1 prospective | Small to medium cumulative effect sizes (*d* = −0.22 to −0.37), showing  diminished cognitive function for chemotherapy group compared to control group, were obtained for each of the eight cognitive domains. | Women who undergo adjuvant chemotherapy may experience subtle cognitive decline. |
| Jim (2012)  [[15](#_ENREF_15)] | K= 17  9 cross sectional  8 prospective | Chemotherapy group performed worse than non-cancer controls in verbal ability (g= -0.19, p<0.01) and worse than no chemo in visuospatial ability (g= 0.27, p<0.01).  Age, education, time since treatment, and endocrine treatment did not moderate observed cognitive deficits in verbal ability or visuospatial ability. | Observed cognitive deficits in patients with breast cancer previously treated with chemotherapy are small in magnitude and limited to domains of verbal and visuospatial ability. |
| Ono (2015)  [[8](#_ENREF_8)] | K= 27  14 cross sectional  5 prospective  8 both | Each cognitive domain produced small effect sizes for cross-sectional and prospective longitudinal studies (ranging from -0.25 to 0.41).  Cross-sectional studies: significant association between adjuvant chemotherapy and cognitive impairment that held across studies with varied methodological approaches.  Prospective studies: cognitive functioning improved over time after receiving adjuvant chemotherapy.  Greater cognitive impairment was reported in cross-sectional studies comparing chemotherapy group with healthy control group. | Cognitive impairment is present among breast cancer patients irrespective of a history of chemotherapy. |

**Table 2.** Neuropsychological measures assigned to specific cognitive domains by the included studies

|  |  |
| --- | --- |
| **Domain** | **Tests used in included studies** |
| Attention/Working memory/Concentration | Trail Making Test Part A  WAIS-III Digital symbol  WAIS-III Digit span  WAIS-III Number/Letter sequencing  WAIS-III Arithmetic; Consonant trigrams  WMS-III Spatial span  WAIS-R Digit span  WAIS-R Arithmetic  Spatial span  Letter/number sequencing  Digit span  PASAT  N-back |
| Executive Functions | PASAT  Trail making B  WCST  MAE COWA  Trail making test Part B  Booklet category test  WAIS-R similarities  The Stroop task |
| Information Processing Speed | WAIS-III Symbol Search  WAIS-III Digit Symbol Coding  Trails Part A  WAIS-R Digit symbol  Letter cancellation task  Trail Making Test (D-KEFS), Color-Word Inference Test; (D-KEFS)  Grooved Pegboard |
| Motor Speed | Grooved peg board  Fepsy Finger tapping |
| Verbal Ability/ Language Function/Language | COWA (FAS)  Boston naming  Vocabulary (WASI, Verbal Fluency Test (Delis Kaplan Executive Function System [D-KEFS]) |
| Verbal Memory/Learning | Buschke selective reminding test  AVLT recall  WMS logical memory, immediate and delayed  CVLT-II, Logical memory I and II (Wechsler memory scale-III [WMS-III])  CVLT-II  WMS-III Logical memory II  VSRT Long-term storage  VSRT delayed recall  Four word short term memory test (4WSTM) - 5s; 15s; 30s  RAVL - total score; trial 6; delayed call |
| Visual Memory/Learning | Benton visual retention test  Faces I and II (WMS-III)  (Rey) Complex figure, immediate and delayed recall  RVLT  WMS-III Family pictures II  NVSRT Long-term storage  NVSRT delayed recall |
| Visuospatial ability | WAIS-III Block design  WAIS-R Block design  RCF – copy |
| Sorting  Distractibility  Reaction time | Sorting Test (D-KEFS)  CPT  CPT  Block Design |
| **Abbreviations used:** PASAT = Paced Auditory Serial Addition Test, WAIS = Wechsler Adult Intelligence Scale, WCST = Wisconsin Card Sorting Test, WMS = Wechsler Memory Scale, D-KEFS = Delis–Kaplan Executive Function System, COWA = Controlled Oral Word Association, CVLT = California Verbal Learning Test, 4WSTM= Four word short term memory test, RAVL = Rey Auditory Verbal Learning, VSRT = Verbal Selective Reminding Test, AVLT = Auditory Verbal Learning Test, RVLT = Rey Verbal Learning Test, RCF= Rey Complex Figure Test, NVSRT = Nonverbal Selective Reminding Test, CPT = | |

**Table 3.** Assignment of neuropsychological measures to specific cognitive domains for the analysis

– ***VERIFY AFTER INCLUDED STUDIES DETERMINED AND KATHREEN IDENTIFIES WHICH TESTS GO HERE***

|  |  |
| --- | --- |
| **Domain** | **Tests used in categorizing domain\*** |
| Attention/Working memory/Concentration | Trail Making Test Part A  Auditory Consonant Trigrams  WAIS (-III and R) Arithmetic, Digit span (forwards, backwards), Letter/Number sequencing  WMS-III Digit span (forwards, backwards), Letter/number sequencing, Spatial Span  D-KEFS Trail Making Test – Condition 2,3  4WSTM – 5s, 15s, 30s  PASAT  N-Back  CPT |
| Executive Functions | Trail Making Test Part B  Stroop  D-KEFS Trail Making Test – Condition 4; Color-Word Inference test – Inhibition and Inhibition/Switching; Sorting Test  WCST  Booklet Category Test  WAIS-R Similarities |
| Information Processing Speed | WAIS (-III, R) Digit symbol, Symbol Search  Letter cancellation  D-KEFS Trail Making Test – Condition 1; Color-Word Interference test – Color Naming and Word Reading |
| Motor Speed | Grooved Pegboard  Fepsy Finger Tapping  DKEFS Trail Making Test – Condition 5 |
| Verbal Ability/ Language Function/Language | COWA (FAS)  Boston Naming Test  D-KEFS Verbal Fluency  WASI Vocabulary |
| Verbal Memory | CVLT (-II) Trial I, Delayed recall, Delayed recognition  WMS-III Logical memory I & II  RAVL total score, trial 6, delayed call  VSRT long-term storage, delayed recall |
| Visual Memory | RVLT Trial I, delayed recall, delayed recognition  RCF Immediate recall, delayed recall  Benton visual retention test  WMS-III Family pictures II, Faces I and II  NVSRT |
| Visuospatial ability | WAIS (-III, R) Block design  RCF – Copy trial |
| Attention/Working memory/Concentration | Trails A  Consonant trigrams  WAIS (-III and R) Arithmetic, Digit span (forwards, backwards), Letter/Number sequencing  WMS-III Digit span (forwards, backwards), Letter/number sequencing  D-KEFS Trail Making Test – Condition 2  4WSTM – 5s, 15s, 30s |
| Executive Functions | Trail making B  Stroop  D-KEFS Trail Making Test – Condition 4, Color-Word Inference test |
| Information Processing Speed | WAIS (-III, R) Digit symbol  WAIS (-III, R) Digit symbol coding  Letter cancellation |
| Motor Speed | Grooved Pegboard |
| Verbal Ability/ Language Function/Language | COWA (FAS)  Boston Naming Test  D-KEFS Verbal Fluency |
| Verbal Memory | CVLT (-II) Trial I, Delayed recall, Delayed recognition  WMS-III Logical memory I & II  RAVL total score, trial 6, delayed call  VSRT long-term storage, delayed recall |
| Visual Memory | RVLT Trial I, delayed recall, delayed recognition  RCF Immediate recall, delayed recall |
| Visuospatial ability | WAIS (-III, R) Block design |
| \* Suggested Domains with Higher Frequency Use Tests. Domain assignment of the neuropsychological tests was determined through current recommendations in the literature and APA policy on meta-analyses [[27](#_ENREF_27), [28](#_ENREF_28)] | |

**Table 4.** Characteristics of participants in included studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First author  (Year) | Chemo (n) | Control type (n) | Radiation (%) | Endocrine tx (%) | Mean Age (y) | Mean Education (y) | Times of NS assessment | Mood assessment | Outcome |
| Collins (2009)[[29](#_ENREF_29)] | 53 | HT 40 |  | T1: 27%  T2: 88% | 57.9 (3.7) | 14.6 (3.2) | T0: Pre-chemo  T1: ~1mo after chemo  T2: ~1y after T1 | Depression– dejection  Fatigue - inertia  Tension - anxiety |  |
| Bender (2006)[[30](#_ENREF_30)] | 19 | No-chemo DCIS 12  (Chemo+  tam 15) |  |  | 40.11 (6.52) | 14.11 (2.28) | T0: Pre-chemo  T1: within 1wk after chemo  T3 = 1y after T2 | Perceived |  |
| Fan (2005)[[16](#_ENREF_16)] | 100 | Healthy 100 | T0: 6.7%  T1: 68%  T2: 65.4% | T0: 4.8%  T1: 62.6%  T2: 66.7% | 48 | 60% post-sec | T0= Initial  T1= 1y  T2= 2y | FACT-F, FACT-ES, FACT-G |  |
| Wefel (2004)[[31](#_ENREF_31)] | 18 |  | 33% |  | 45.4 (6.7) | 14 (2.6) | T0: pre-chemo  T1: ~6 mos after T0  T2: ~18 mos after T0 | FACT |  |
| Tager (2010)[[17](#_ENREF_17)] | 30 | No-chemo 31 | 56.7% |  | 60.3 (5.6) | 16.6 (3.2) | T0: Pre-chemo  T1: ~6 mos after T0  T2: 6 mos after T1 | Beck depression Inventory  Zung anxiety index |  |
| Jenkins (2006)[[18](#_ENREF_18)] | 85 | No-chemo 43  Healthy 49 |  |  | 51.49 (9.57) | 12.02 (2.60) | T0: Baseline,  T1: 4wks after chemo  T2: 12mos after chemo | GHQ |  |
| Ahles (2010)[[19](#_ENREF_19)] | 60 | No-chemo 72  Health 45 |  |  | 51.7 (7.1) | 15.7 (2.7) | T0: Pre- chemo  T1: 1mo after chemo  T2: 6 mos after chemo  T3: 18 mos after chemo | CES – depression  STAI State Anxiety  FSI Fatigue |  |
| McDonald (2012)[[32](#_ENREF_32)] | 16 | No chemo 12  Healthy 15 | Chemo: 68.75%  No chemo: 83.33% |  | 52.9 (8.6) | 15.2 (2.6) | T0: Pre-radiation, chemo  T1: 1 mo after chemo  T2: 1y after chemo |  |  |

**Table 5.** Weighted mean effect sizes for each study

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | k | Effect size (SE) | 95% CI | z | Q |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**Table 6.** Weighted mean effect sizes of neuropsychological tests and heterogeneity for each cognitive domain

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Cognitive Domain | # of studies | Weighted pooled effect size | n | 95% CI | Fail-safe N |
| Attention |  |  |  |  |  |
| Executive Functions |  |  |  |  |  |
| Information Processing Speed |  |  |  |  |  |
| Motor Speed |  |  |  |  |  |
| Verbal Ability |  |  |  |  |  |
| Verbal Memory |  |  |  |  |  |
| Visual Memory |  |  |  |  |  |
| Visuospatial ability |  |  |  |  |  |

**Table 7.** Meta-analytic regression results for moderator variables

|  |  |  |
| --- | --- | --- |
| **Table 3:** **PRISMA-P 2015 checklist: recommended items to include in a systematic review protocola** | | |
| **ADMINISTRATIVE INFORMATION** | | |
| **Section/topic** | **Item #** | **Checklist item** |
| **Title** |  |  |
| **Identification** | 1a | Identify the report as a protocol of a systematic review |
| **Update** | 1b | If the protocol is for an update of a previous systematic review, identify as such |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number |
| **Authors** | | |
| **Contact** | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author |
| **Contributions** | 3b | Describe contributions of protocol authors and identify the guarantor of the review |
| **Amendments** | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments |
| **Support** | | |
| **Sources** | 5a | Indicate sources of financial or other support for the review |
| **Sponsor** | 5b | Provide name for the review funder and/or sponsor |
| **Role of sponsor/funder** | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol |
| **INTRODUCTION** | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) |
| **METHODS** | | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated |
| **Study records** | | |
| **Data management** | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review |
| **Selection process** | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) |
| **Data collection process** | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale |
| **Risk of bias in individual studies** | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis |
| **Data** | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized |
| 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I2, Kendall’s tau) |
| 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) |
| 15d | If quantitative synthesis is not appropriate, describe the type of summary planned |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) |

PRISMA-P Preferred Reporting Items for Systematic review and Meta-Analysis Protocols.

aIt is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration [[30](http://www.systematicreviewsjournal.com/content/4/1/1#B30)] for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution License 4.0.

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