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Chemotherapy-Related Cognitive Dysfunction in Breast Cancer Survivors: A Systematic Review

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Abstract: *Objectives*: The major aims of this integrative review were to identify: 1) specific cognitive domains affected by chemotherapy; 2) predictors of cognitive dysfunction related to chemotherapy; 3) reported underlying mechanisms of chemotherapy-related cognitive dysfunction, and 4) clinical and research implications of chemotherapy-related cognitive dysfunction (CRCD) among breast cancer survivors. *Methods*: A computerized search of published research articles through the health journal databases of PubMed, CINAHL, EMBASE, and Web of Science was performed by using the keywords "chemotherapy," "cognitive dysfunction," "cognitive impairment," "cognitive decline," "breast cancer," and "breast carcinoma." References were screened according to inclusion and exclusion criteria. *Results*: After screening the titles and abstracts of 639 articles, 20 research studies were identified that focused on chemotherapy-related cognitive dysfunction in breast cancer for the final analysis. The 20 studies included: one longitudinal study, eleven prospective studies, two case-control studies, two retrospective studies, and four cross-sectional studies. The analysis of these 20 research studies contributed new knowledge about cognitive domains being affected by chemotherapy, risk factors for CRCD and underlying mechanisms of CRCD. *Conclusion*: This systematic review indicates significant clinical implications of early assessment and early interventions for CRCD to assist breast cancer survivors.

Keywords: Chemotherapy, Cognitive Dysfunction, Breast Cancer

1. Introduction

Breast cancer is one of the leading cancer among women in the United States, with an estimated 276,480 cases of invasive breast cancer (BC) and 48,530 cases of non-invasive BC diagnosed in 2020 alone [1]. Chemotherapy is used to destroy and eliminate cancer cells for early-stage invasive and late-stage BC [2]. Early screening and treatment for BC have improved the prognosis for breast cancer survivors (BCSs) compared to other cancers, resulting in an increased 5-year survival rate of 91%, a 10-year survival rate of 84%, and a 15 years survival rate of 80% [3]. Although chemotherapy treatment increases survival rates, chemotherapy often results in "chemotherapy-related cognitive dysfunction" (CRCD) or cognitive impairment that significantly affects breast cancer survivors' quality of life (QOL) [4].

According to the International Cognition and Cancer Task Force (ICCTF), 13%-70% of cancer patients are affected by CRCD [5]. Cognitive impairment, often described by BCSs' as "chemo-brain," varies from 20% to 90%, beginning when chemotherapy is initiated and persisting up to 10 years after treatment [6-9]. Current evidence and data indicate that changes in cognitive functions, such as 1) memory; 2) executive function; 3) processing speed; 4) visual, spatial, and constructional ability; 5) attention and concentration; 6) reaction time; and 7) motor speed and dexterity, as measured by standardized neuropsychological tests, are associated with adjuvant chemotherapy treatment [7, 8, 10-12]. Breast cancer survivors may suffer from CRCD or chemo-brain during or after chemotherapy [13, 14]. Although evidence shows an association between cognitive dysfunction and chemotherapy among BCSs, research gaps remain in this area. Specifically, there is a gap in

evidence related to the relationship between (1) CRCD and the cognitive domains that have been affected [15]; (2) CRCD and predictors such as patient age, stage of breast cancer, and chemotherapy agents [16-18], pre-existing depression and anxiety [19]; and (3) CRCD and underlying mechanisms [20].

The overall goal of this systematic review is to identify evidence related to the impact of chemotherapy on cognitive dysfunction among BCSs through a comprehensive review of the recent ten years of published clinical research studies. This review also addresses research gaps identified above and discusses clinical and research implications of chemotherapy-related cognitive dysfunction for BCSs.

2. Methods

2.1. Search Strategy

The search was limited to current research studies published within the past ten years from January 2009 to January 2020. The systematic search was conducted in the health journal databases of PubMed/MEDLINE, CINAHL, EMBASE, and Web of Science. The search included specified Medical Subject Headings (MeSH) terms and keywords related to chemotherapy-related cognitive dysfunction in breast cancer survivors. MeSH terms utilized were "chemotherapy", "drug therapy", "cognitive dysfunction", "cognitive impairment", "cognitive decline", "breast cancer", "breast carcinoma", and "breast tumors". All publications were screened to retrieve the abstracts and full-text articles by using the selection criteria. The search strategy used for the database PubMed/MEDLINE (Table 1) was also used for the other electronic health journal databases described above. Additional related published articles were identified by reviewing the reference lists from eligible full-text articles.

Table 1. *PubMed/MEDLINE Search Strategy.*

1. “Cognitive dysfunction” [MeSH] OR “cognitive impairment” OR “cognitive decline”
2. "Chemotherapy" [MeSH] OR "drug therapy"
3. "Breast cancer" [MeSH] OR "breast carcinoma" OR "breast tumors"
4. 1 AND 2 AND 3

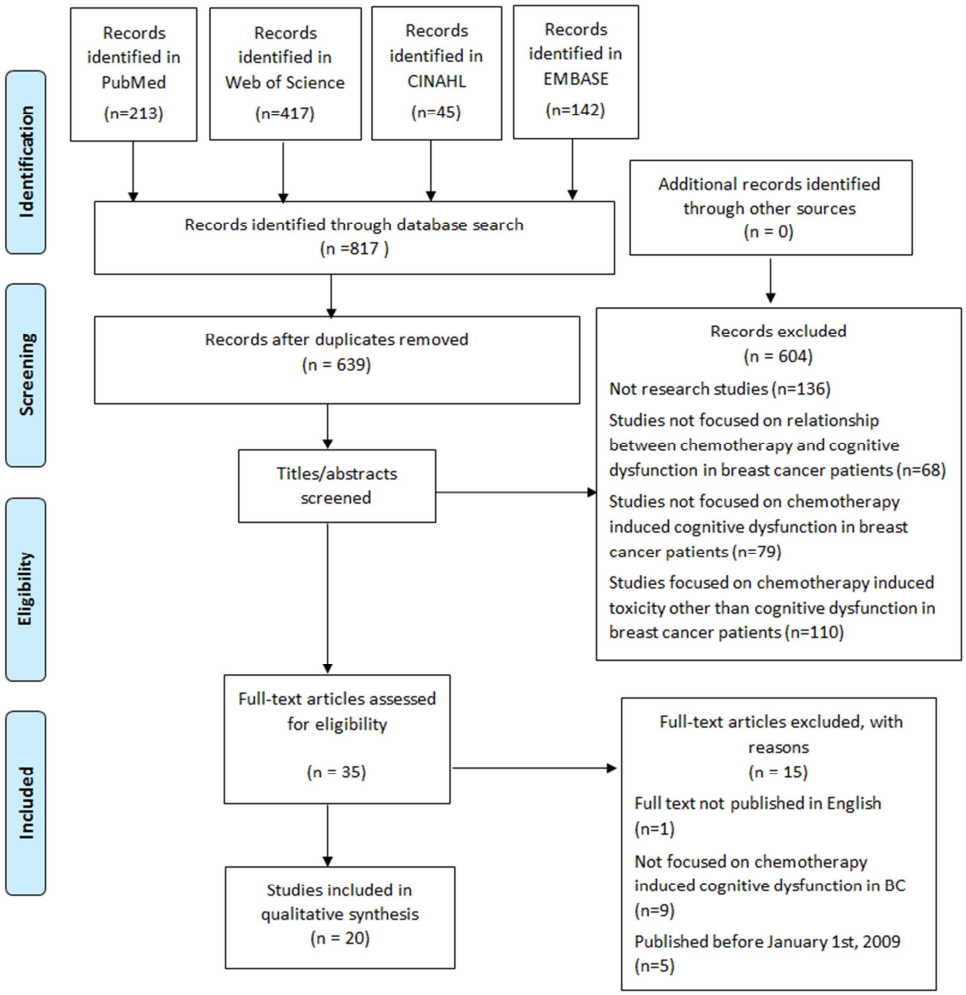

Figure 1. *A PRISMA flowchart of the selection process.*

2.2. Study Selection

EndNote X9 was used as the reference management software package to manage all the research study citations. Screening study titles and abstracts were followed as the next step for potential articles and then reviewing full-text articles to decide if the article met the inclusion criteria. Inclusion criteria included: 1) research focused on the relationship between chemotherapy and cognitive dysfunction in BCSs who exposed to chemotherapy with any stage of cancer; 2) original publications; 3) publications in peer-reviewed journals; 4) publications in English; and 5) publications published between January 2009 to January 2020. Exclusion criteria included: 1) non-research articles; 2) not published in English; 3) research not focused on the relationship between chemotherapy and cognitive dysfunction in BCS; and 3) research focused on CRCD in breast cancer published before January 1, 2009.

Study designs qualified for inclusion were randomized controlled trials (RCTs), longitudinal studies, cohort studies (prospective observational studies), cross-sectional studies, case-control studies, and retrospective analytical studies. The entire study population was restricted to breast cancer women who initiated, were in the process, or had finished chemotherapy. Studies included research conducted in US and other countries if published in English. Studies were not eliminated if they met the inclusion criteria. Studies were eliminated if they met the exclusion criteria. Two authors reviewed the chosen articles. When there was a conflict, they would go back to the original article and double-check to make sure it meets all the inclusion criteria.

After applying the inclusion and exclusion criteria to the titles and abstracts of the initial search, 35 articles met the inclusion criteria. Full-text PDF were obtained for all the articles and were reviewed carefully by the authors. After a review of articles for inclusion, 20 articles were included. The remaining 15 articles were eliminated because they did not meet all the inclusion criteria. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart is presented in Figure 1 in this paper to show the selection process.

2.3. Data Extraction

A literature review table was implemented to extract data identifying the first author, year published, study design, study setting, research intervention, sample characteristics, outcome measures, and findings (see Table 2).

Table 2. *Summary of the Studies related to Chemotherapy-Related Cognitive Dysfunction in Breast Cancer.*

First Author and Year Published	Study Design and Setting	Intervention	Sample Characteristics	Outcome Measures	Findings/Results
Ahles, 2010	A longitudinal prospective study. Participants were recruited from the Breast Cancer Service of the Norris Cotton Cancer Center in the United States.	Systemic chemotherapy or surgery and/or local, non-CNS radiotherapy as first treatment for BC women.	N=60 Mean age: 51.7 years (SD: 7.1 years) (range 31-66) Race/ethnicity: White (98%) Asian (2%) Hispanic (2%) Diagnosis: noninvasive (state 0) or invasive (stage I, II, or III A) breast cancer.	Verbal ability was evaluated by VFT, verbal memory was evaluated by CVLT-II, LM I and II, visual memory was evaluated by Faces I and II, working memory was evaluated by PASAT, processing speed was evaluated by digit symbol-coding, TMT, C-WIT and GP, sorting was evaluated by ST, distractibility was evaluated by CPT and Reaction time.	Breast cancer women experienced chemotherapy (N=60) had lower processing speed performance compared with patients without chemotherapy and HCs. Patients' age and pretreatment cognitive reserve were considered to be associated with the decline in Processing Speed. chemotherapy was also found to have a short-term impact on patients' verbal ability.
Biglia, 2012	A prospective cohort study. Participants were recruited from the San Giovanni Battista Hospital of Turin in Italy.	Cognitive assessment was done for BC women before and after 6 months of chemotherapy. Emotional evaluation was done for BC women before and after 1, 3, and 6 months of chemotherapy.	N=40 Mean age: 51 years (SD, 7.81 years) (range 38-65) Race/ethnicity: Not disclosed (100%) Diagnosis: breast cancer without depression.	Premorbid intelligence was evaluated by using a language related tests, the BIT, which is the Italian version of the NART. Patients' cognitive function was tested by using 10 neuropsychological tests: MMSE, AM, DSF, TMT, PWF, SSIR, SSDR, RAVLT	Breast cancer women who had chemotherapy showed a worsening in MMSE (N=12), AM (N=6) and TMT (N=40) tests. The cognitive domain of attention was specifically affected by chemotherapy. The

First Author and Year Published	Study Design and Setting	Intervention	Sample Characteristics	Outcome Measures	Findings/Results
				immediate recall, RAVLT delayed recall, RPM.	objective cognitive deterioration is independent from the patient's emotional status. Depression and anxiety are associated with patient self-perceived cognitive dysfunction.
Bower, 2013	A cross sectional study. Participants were recruited from the Los Angeles County Surveillance, Epidemiology, and End Results registry in the United States.	Primary cancer treatment (surgery, radiotherapy, and/or chemotherapy) was done to BC women with stage 0 to III A breast cancer within the past 3 months. Patients not yet started endocrine therapy.	N=171 (50% CT, 50% Non-CT) Mean age: 51.5 years Race/ethnicity: White (80%) Other (20%) Diagnosis: breast cancer with no neurologic or immune-related medical conditions or behaviors known to influence the immune system (e.g., smoking, heavy drinking).	Fatigue was assessed using the MFSI-Short Form. The BDI-II was used to assess depression symptoms. The PSQI was used to assess subject sleep quality. The SMQ was used to assess cognitive complaints. Peripheral-blood leukocytes was used to extract Genomic DNA and the DNA was assayed by a commercial TaqMan Genotyping Assay.	The result of this study shows that in the immediate aftermath of breast cancer treatment, women with high-expression variants of multiple cytokine genes was found to be at particular risk for fatigue. The additive composite of high-expression alleles in IL6, TNF, and ILB could be used as a simple clinical genetic biomarker of risk for fatigue potentially. Significantly higher levels of memory complaints and depression were also reported by women with more high-expression alleles.
Cerulla, 2017	A prospective longitudinal study. Patients were recruited in Consorci Sanitari de Terrassa Hospital and Corporacio Sanitaria Parc Tauli Hospital in Spain.	A combination of FEC alone (6 cycles of FEC) or with taxanes (FEC + T) (4 cycles of FEC plus 8 cycles of taxanes) were used to treat BC women compared at three time points: before chemotherapy, after chemotherapy completion (short-term evaluation), and at a mean of 74.5 weeks from baseline (long-term evaluation).	N=51 (FEC=26 and FEC+T=25) Mean age of FEC: 50.5 years (SD, 8.8 years) Mean age of FEC+T: 52.5 years (SD, 7.8 years) (range 18-70) Race/ethnicity: Not disclosed (100%) Diagnosis: breast cancer with no metastatic disease, no neurologic or acute psychiatric disorders.	A trained neuropsychologist who was blind to the treatment group assessed participants by using a battery of neuropsychological test and anxiety, mood, and fatigue questionnaires. The same order was followed when giving assessment and questionnaires. The assessment lasted approximately 3 hours with a brief break in the middle of the test.	Compared with baseline evaluation in CVLT delayed recall, TMT-A and Letter-number tests, breast cancer women (N=51) with chemotherapy showed a worsening on cognitive assessment at short-term follow up. Treatment with a regimen of FEC altered cognitive function. The cognitive performance at the end of cycles is worse with FEC plus taxane. Cognitive impairment is also found long time

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Deprez, 2012	A longitudinal study. Patients were recruited from University Hospital Gasthuisberg, Belgium.	Adjuvant chemotherapy FEC (6 cycles), FEC (3 cycles) plus paclitaxel (3 cycles) were used to treat early-stage BC women (N=34). These women were compared with other early-stage breast cancer women (N=18) without chemotherapy and 22 matched healthy controls.	N=34 (FEC or FEC + paclitaxel) Mean age: 43.7 years Race/ethnicity: Not disclosed (100%) Diagnosis: breast cancer (stage I 17.6%, stage II 55.9%, stage III 26.5%). No history of psychiatric disorders, neurologic condition and brain injury. N=16 (BC with no chemotherapy) Mean age: 43.1 years Race/ethnicity: Not disclosed (100%) Diagnosis: breast cancer (stage I 81.3%, stage II 18.7%). No history of psychiatric disorders, neurologic condition and brain injury. N=19 (HCs) Mean age: 43.8 years Race/ethnicity: Not disclosed (100%)	The CFQ was used to assess self-reported cognitive functioning which provided subscales on distraction, distraction in social situations, names and word finding, orientation, and a total summary score. The STAI and BDI were completed by all participants. A Dutch version of the NART was used to evaluate verbal IQ. Neuropsychologic evaluation and magnetic resonance imaging scans were done on the same day. A 3T scanner with an 8-channel phased-array head coil was used for participants. Explore DTI was used for DTI preprocessing.	after treatment. At 3 to 4 months after treatment, BC women with chemotherapy (N=34) reported a significant increase in cognitive complaints in distraction, names and word finding, and CFQ total score. The neuronal substrate of CRCD may be evaluated sufficiently by the diffusion tensor imaging (DTI)-based assessment of the microstructural properties of white matter (WM). Patients exposed to chemotherapy showed longitudinal changes in cerebral WM by comparing fractional anisotropy (FA) values of DTI images taken before and after treatment. FA changes may serve as a neuropathologic biomarker for chemotherapy-related neurotoxicity.
Jansen, 2011	A prospective longitudinal study. Participants were recruited from two outpatient oncology clinics of a large health maintenance organization in the San Francisco Bay Area, United States.	A doxorubicin and cyclophosphamide regimen alone or followed by a taxane were used to treat BC women.	N=71 Mean age: 50.3 years (SD: 8.8 years) (range 30-65) Race/ethnicity: Caucasian (43.7%) Asian/Pacific Islander (40.9%) African American (7.0%) Hispanic (5.6%) Other (2.8%) Diagnosis: Early-stage breast cancer.	The RBANS and GPT were used to assess cognitive function. The ST was used to evaluate executive function. The AFI was used to evaluate potential covariates, the CES-D was used to assess depression, the STAI-S was used to evaluate anxiety, and the LFS was used to assess severity of fatigue.	A decrease of one or more SDs for the RBANS, ST, GP tests was found in BC women with chemotherapy (N=35). Cognitive impairment may associated with the BC diagnosis and chemotherapy may have a negative impact on cognitive function. CRCD is more acute than chronic side effects of therapy.
Jung, 2017	A prospective cohort study. Participants were recruited from the University of	Two groups of women surgically treated for BC received adjuvant chemotherapy (Doxorubicin plus Cyclophosphamide 4%; Doxorubicin plus Cyclophosphamide plus Paclitaxel 79%; Docetaxel plus Cyclophosphamide 18%)	N=28 (CT) Mean age: 49.68 years (SD, 9.74 years) N=34 (non-CT) Mean age: 53.94	During fMRI scanning, BC women were prospectively assessed with neurocognitive evaluations followed	A worse overall VWMT score and greater spatial variance was found at 7 months after chemotherapy in

First Author and Year Published	Study Design and Setting	Intervention	Sample Characteristics	Outcome Measures	Findings/Results
	Michigan Comprehensive Cancer Center in the United States.	over one year or radiotherapy without chemotherapy (non-CT) and age-matched HCs with negative mammograms.	years (SD, 8.42 years) N=30 (HC) Mean age: 51.13 years (SD, 8.47 years) Race/ethnicity: White: 79% (CT), 91% (non-CT), 87% (HC) Non-white: 21% (CT), 9% (non-CT), 13% (HC) Diagnosis: breast cancer stage 0-IIIA without cognitive disorder, no depression and secondary diagnosis of psychiatric or neurological disorders.	by self-report questionnaires at three time points. About one month (24-36 days) after surgery and before chemotherapy, radiotherapy/endocrine therapy, baseline (M0) evaluation was done. About five months (M5) following baseline and at least one month after chemotherapy, the second evaluation was done. About one year (M12) post-baseline, the third evaluation was done.	BC women (N=28) than the HCs. For chemotherapy patients, neural inefficiency and cognitive impairment in executive network usually persisted over the following months. Chemotherapy is an independent predictor in neurocognitive impairment of the executive network at one year. In contrast, patient self-reported cognitive dysfunction was independently predicted by physical and psychological symptoms.
Kesler, 2013	A cross-sectional study. Participants were recruited via the Army of Women and local media advertisements by the Stanford Cancer Institute in the United States.	BC women with stage I-IIIA cancer who had surgery and adjuvant chemotherapy (doxorubicin + cyclophosphamide or paclitaxel; cyclophosphamide + 5-fluorouracil and paclitaxel or methotrexate) 1 to 12 years after therapy were evaluated and compared with healthy controls.	N=42 (BC) Mean age: 54.6 years (SD, 6.5 years) N=35 (HC) Mean age: 55.5 years (SD, 9.3 years) Race/ethnicity: Not disclosed (100%) Diagnosis: Stage I-IIIA BC without psychiatric disorders.	The MMQAS and HVLT-R were used to assess memory function. The CAD was used to measure depression level. MRI scanning was performed on whole body scanner. Preprocessing and hippocampal volume measurement were done in Freesurfer v 4.5. A high sensitivity multiplexed sandwich immunoassay was used to measure cytokine level.	Reduced HVLT Total and Delayed recall performances and reduced MMQ scores were found in BC women with chemotherapy (N=42). Chemotherapy induced inflammation may contribute to hippocampal changes that underlie the CRCD. Left hippocampal volumes and memory function were decreased significantly and interleukin-6 (KL-6) and tumor necrosis factor-alpha (TNFα) concentrations were increased significantly in the BC group.
Kesler, 2016	A retrospective, cross-sectional study. Email listserv, community flyer postings, internet, physician referrals, and local cancer	4 to 8 cycles of standard dose anthracycline-based (doxorubicin, cyclophosphamide, paclitaxel, fluorouracil) and 4 to 8 cycles of standard dose non-anthracycline (cyclophosphamide, paclitaxel, methotrexate, fluorouracil) chemotherapy were used to treat BC women. Participants have completed their primary cancer treatment of surgery,	N=20 (anthracycline) N=19 (Non-anthracycline) N=23 (No chemotherapy) Mean age: 54.7 years (SD, 8.5 years) Race/ethnicity: Not disclosed (100%)	Verbal memory was assessed by the HVLT-R. The WCST or CTMT were used to measure executive function. The D-KEFS or COWA was used to assess verbal fluency. The BRIEF, CAD were also	A lower verbal memory function was found in BC women with anthracycline-based chemotherapy (N=20) than the other two groups. Compared with the non-chemotherapy

First Author and Year Published	Study Design and Setting	Intervention	Sample Characteristics	Outcome Measures	Findings/Results
	support group advertisements were used to recruit participants in the United States.	radiotherapy and chemotherapy more than 6 months before they enrolled in this study. They were compared with primary BCSs without chemotherapy.	Diagnosis: breast cancer stage I-IIIA without psychiatric, neurologic, or comorbid medical conditions that may affect cognitive ability or major sensory deficits.	administered. All participants need finish a patient reported measure of depression, anxiety, and fatigue.	patients, chemotherapy patients reported more complaints in executive function difficulties and psychological symptoms. Compared with none-anthracycline agents, anthracycline-based agents may have higher negative effects on specific cognitive domains and brain network connections.
Klemp, 2018	A prospective cohort study. Patients were recruited from the University of Kansas Medical Center in the United States.	BC women receiving chemotherapy were evaluated prospectively for changes of subjective and objective cognitive performance and QOL at four time points: prior to chemotherapy (T1), after cycle 3 of chemotherapy (T2), within 2-3 weeks of completing chemotherapy (T3) and 8+ years later (T4).	N=20 (T1) Mean age: 43.15 years (SD, 5.82 years) N=16 (T4) Mean age: 53 years (SD, 4.62 years) Race/ethnicity: Caucasian (85%) African American (5%) Hispanic (10%) Diagnosis: breast cancer (stage I 55%, stage II 30%, stage III 5%, stage IV 5%, not reported 5%).	The HSCS was used to assess objective cognitive function (T1, T3, T4). Subjective measures for cognitive function, depression, fatigue and mental and physical QOL were evaluated at all time points. The FACT-C and the MDACI item were used for neuropathy at T4.	A significant decline over time for the BCPT Cognitive Problems Scale was found in BC women with chemotherapy (N=20). A significant worsening of cognitive performance over the course of treatment that was accompanied by fatigue and depression was found in pre-and peri-menopausal women. Many participants reported depression more than 8 years after chemotherapy.
Miao, 2016	A cross-sectional study. Participants were recruited from the First Affiliated Hospital of Anhui Medical University in China.	Standard-dose chemotherapy (taxotere/Adriamycin/cyclophosphamide) was used to treat BC women. Participants were evaluated within one month after chemotherapy and compared with healthy controls.	N=22 (BC) Mean age: 43.68 years (SD, 6.81 years) N=22 (HC) Mean age: 44.5 years (SD, 7.44 years) Race/ethnicity: Chinese (100%) Diagnosis: primary BC stages II-III without metastatic disease.	Each participant was required to complete the neuro-psychological background tests within approximately 1 hour. The MoCA test was conducted to assess general cognitive function. The Chinese version of the CRF test was performed to evaluate fatigue symptoms, and the HDRA and HARS were performed respectively to assess the participant's potential depression and anxiety symptoms.	A significantly worse performance in the SC, SW, and SI tests was found in BC women with chemotherapy (N=22). There was also a significantly lower connectivity within the subsystem of dorsal medial prefrontal cortex and medial temporal lobe. The functional disconnection of the subsystem of medical temporal lobe could be a contributing factor associated with cognitive impairment,

First Author and Year Published	Study Design and Setting	Intervention	Sample Characteristics	Outcome Measures	Findings/Results
Menning, 2016	A prospective cohort study. Participants were recruited from Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, VU University Medical Center, Flevoziekenhuis, Reinier de Graaf Gasthuis, and Academic Medical Center Amsterdam in Netherlands.	Adjuvant anthracycline-based chemotherapy with or without endocrine treatment were used to treat BC women. They were compared with BC women who did not require systemic treatment and age-matched cancer free HCs.	N=31 (BC+SYST) Mean age: 49.8 years (SD, 9.16 years) N=24 (BC) Mean age: 51.2 years (SD, 6.8 years) N=33 (No-cancer control) Mean age: 51.4 years (SD, 8.3 years) Race/ethnicity: Not disclosed (100%) Diagnosis: breast cancer stage 0 to stage III	Neuropsychological tests were used to assess cognitive function on 18 tests grouped into eight cognitive domains at two time points: before chemotherapy (T1) and six months after chemotherapy (T2), or at similar intervals. Health-related QOL, depression, anxiety, stress, mood, and cognitive problems were also evaluated.	especially in the attention domain after chemotherapy. BC women with chemotherapy (BC+SYST) (N=5) had cognitive dysfunction at T2 compared to BC women with no systematic treatment (N=1) and HCs (N=2). There is a need for further investigation of the predictive value of demographic and psychosocial factors in cognitive dysfunction in a larger sample of patients with cognitive problems.
Ng, 2017	A multicenter, prospective cohort pilot study. Patients were recruited at the National Cancer Centre Singapore and KK Women's and Children's Hospital in Singapore.	Anthracycline-based chemotherapy (56.9%) and Taxane-based chemotherapy (43.1%) were used to treat BC women with early-stage cancer.	N=51 Mean age: 52.6 years (SD, 9.5 years) Race/ethnicity: Chinese (78.4%) Malay (7.8%) Indian (11.8%) Other (2.0%) Diagnosis: early-stage BC.	The validated FACT-C was used to evaluate patient self-perceived cognitive dysfunction across three time points: prior to chemotherapy (T1), during chemotherapy (T2), and after chemotherapy (T3). The enzyme-linked immunosorbent assay was used to quantify plasma brain-derived neurotrophic factor levels. The Sanger Sequencing was used for genotyping.	Subjective cognitive dysfunction was reported by post chemotherapy BC women (N=11). A statistically significant change in brain-derived neurotrophic factor levels was found after chemotherapy which was related to self-perceived deficit of concentration. Brain-derived neurotrophic factor levels were similar over time among carriers of the Met homozygous carriers of the brain-derived neurotrophic factor rs6265 polymorphism.
Piccirillo, 2015	A case-control study. Participants were recruited from Siteman Comprehensive Cancer Center at Barnes-Jewish Hospital in the United States.	BC women who completed standard adjuvant chemotherapy within two years at least 30 days before enroll in this study. Women who reported cognitive dysfunction were considered to be cases and women who reported no cognitive dysfunction were considered to be controls.	N=15 (Impaired) Mean age: 54 years (range 36-69) N=13 (Non-Impaired) Mean age: 52 years (range 40-67) Race/ethnicity: White: Impaired 64%, Non-Impaired 60% Black: Impaired 29%, Non-impaired 27%	Participants finished the following evaluation forms: (1) medical history and health information, (2) CFQ, and (3) GRC. Subjects were assigned to the impaired or non-impaired groups based on responses to the GRC.	Cognitive dysfunction by the GRC was reported by BC women with chemotherapy (N=15). Women who self-reported cognitive dysfunction were found to have MRI measured disrupted resting state functional connectivity when

First Author and Year Published	Study Design and Setting	Intervention	Sample Characteristics	Outcome Measures	Findings/Results
			Asian: Impaired 7%, Non-Impaired 13% Diagnosis: invasive ductal or lobular BC stage I-III with no history of brain trauma or disease.		compared to women without cognitive dysfunction. Some women may be more sensitive to the standard treatments which may result in changes in functional connectivity in the brain networks associated with attention and executive function.
Quesnel, 2009	A longitudinal prospective study. Participants were recruited from the CHUQ and Laval University Cancer Research Center in Canada.	41 BC women received standard protocols of chemotherapy which was followed by radiotherapy for 38 of them.	N=41 Mean age: 50.3 years (SD, 7.2 years) (range 35-70) Race/ethnicity: Not disclosed (100%) Diagnosis: Non-metastatic breast cancer stage I to III.	The neuropsychological tests of CFT, RAVLT, TMT, SDMT, DS and VMS Subtests of WMS-R, VFT, and Ruff 2 & 7 were administered. A battery of self-report scales was completed by all the participants. The vocabulary and the picture completion subtests of the WALS-III were used to assess participants' pre-morbid verbal and non-verbal intellectual quotient.	Verbal fluency impairment was found in BC women with chemotherapy compared with patients without chemotherapy. A limited number of cognitive functions were associated with the negative effects of BC treatment. Both chemotherapy and radiotherapy can cause cognitive impairment, but verbal fluency is especially sensitive to the effects of chemotherapy.
Ramalho, 2017	A prospective cohort study. Participants were recruited from the Breast Clinic of the Portuguese Institute of Oncology of Porto in Portugal.	BC women diagnosed in the previous three months treated with neoadjuvant chemotherapy (10.3%) and adjuvant chemotherapy (89.7%): Doxorubicin plus cyclophosphamide (20.7%); Doxorubicin plus cyclophosphamide plus docetaxel (9.9%); 5-FU plus epirubicin plus cyclophosphamide (8.3%), 5-FU plus epirubicin plus cyclophosphamide plus docetaxel (59.5%); others (1.6%).	N=418 Age >55 years old (52.2%) Age≤ 55 years old (47.8%) Race/ethnicity: Not disclosed (100%) Diagnosis: breast cancer (stage zero 6.9%; stage I 47.1%; stage II, 31.6%; stage III, 14.4%). All the patients had no cognitive impairment.	The HADS and MoCA were used for assessments before chemotherapy and at one year after diagnosis. Poisson regressions was used to compute adjusted relative risks and corresponding, 95% CI was used to identify predictors of cognitive dysfunction.	Almost a four-fold higher risk of developing cognitive dysfunction was found in BC women with chemotherapy (N=257) than those without chemotherapy (N=161). The association between cognitive dysfunction and chemotherapy was modified by anxiety at baseline.
Tao, 2016	A cross-sectional study. Participants were recruited from The First Affiliated Hospital of Anhui Medical University in	BC women who had six cycles standard dose of post-operative regular adjuvant chemotherapy (doxorubicin, paclitaxel and cyclophosphamide) without endocrine therapies compared with age and education-matched HCs.	N=33 (BC) Mean age: 39.48 years (SD, 6.32 years) (range 26-52) N=31 (HC) Mean age: 39 years (SD, 7.289 years) (range 26-52)	Participants were assessed using standardized neuropsychological tests created to evaluate their normal cognitive function, executive function, depression, anxiety	Higher scores on the SW and TMTA tests were found in BC women with chemotherapy (N=33) compared to the HCs which illustrates the speed of processing

First Author and Year Published	Study Design and Setting	Intervention	Sample Characteristics	Outcome Measures	Findings/Results
	China.		Race/ethnicity: Chinese (100%) Diagnosis: breast cancer (stage I-III). All the patients had normal cognitive function with a MMSE score of ≥ 24 without subtle or severe affective disorders.	and fatigue levels. The MMSE was administered. All BC women and HCs were assessed. Fatigue symptoms was ruled out by the Chinese version of the CRF. The HDRS and HARS were used to evaluate the potential depression and anxiety levels of participants.	information impairment in BC women. Both neuropsychological tests and functional connectivity have been abnormal in BC women compared to HCs. At the same time, the regions of abnormal brain functional connectivity based on the posterior cingulate cortex were located in the frontal lobes mainly. The decreased functional connectivity has negative effects on performance of neuropsychological tests.
Vardy, 2017	A mechanistic cohort study. Patients were recruited from Princess Margaret Hospital clinic and patient support groups in Toronto, Canada.	BC women were assigned to one of four groups: group received adjuvant or neo-adjuvant chemotherapy and self-reported cognitive impairment (CTh+CS+); group received adjuvant or neo-adjuvant chemotherapy without self-reported cognitive impairment (CTh+CS-); group had not received adjuvant chemotherapy (CTh-); group received chemotherapy with FACT-C score of 86-99 had no further assessment.	N=44 (CTh+CS+) Mean age: 48.39 years (range 30-60) N=52 (CTh+CS-) Mean age: 48.39 years (range 29-60) N=30 (CTh-) Mean age: 54.10 years (range 30-59) Race/ethnicity: Not disclosed (100%) Diagnosis: invasive breast cancer without psychiatric illness, alcohol abuse or co-morbidity that might interfere with neuropsychological function.	Participants finished neuropsychological tests, fMRI, questionnaires and had blood sample drawn. Objective neuropsychological tests included: clinical neuropsychological tests, CANTAB, and the modified SET. The FACT-Cog v2 and the PAFI were used for subjective tests of cognitive function. The FACT-F fatigue subscale was used to assess fatigue in conjunction with the FACT-G which was used to evaluate health-related QOL. Anxiety and depression levels were assessed by the 12-item GHQ.	More cognitive impairment on visual motor co-ordination assessed by the GP test was found in BC women with chemotherapy (N=44) than BC women without chemotherapy. The hypothesis of objective difference in cognitive function between groups was not supported by formal neuropsychological test results, but self-reported impairment was associated with fatigue, anxiety and depression, and lower QOL. Increased levels of IL-8 were related to cognitive dysfunction on clinical tests. Functional imaging showed that brain activation may be modified by chemotherapy with hypoactivation compared to BC women without

First Author and Year Published	Study Design and Setting	Intervention	Sample Characteristics	Outcome Measures	Findings/Results
Xuan, 2017	A case-control study. Participants were recruited in the Department of Oncology of the Affiliated Second Hospital of Anhui Medical University in China.	BC women who had six cycles of standard dose postoperative adjuvant taxotere-epirubicin-cyclophosphamide chemotherapy (IV decetaxel 75 mg/m^2, IV doxorubicin 50 mg/m^2, IV cyclophosphamide 500 mg/m^2, 21 days per cycle compared with age and education-matched HCs.	N=28 (BC) Mean age: 51.46 years (SD, 8.72 years) N=40 Mean age: 50.23 years (SD, 8.15 years) Race/ethnicity: Chinese (100%) Diagnosis: breast cancer infiltrating ductal carcinoma, ECOG score 0-1, stage I to IV without brain metastases and without obvious psychological distress and fatigue.	All participants had source memory tests and resting-state functional MRI scans. Within one month after the last cycle of chemotherapy, neuropsychological tests and MRI scans were done. Graph-based approaches was used to construct and analyze individual whole-brain functional brain networks. All tests were administered by one doctor to avoid bias.	chemotherapy. Significant lower scores on the DS, VFT, MMSE, and the source memory task was found in BC women with chemotherapy (N=28) compared to the HCs. Abnormal organization of large-scale functional brain networks is associated with chemotherapy, which could account for source memory impairment in BC patients.
Yamada, 2010	A retrospective study. Participants were recruited from Iowa Cancer Registry in the United States.	A standard multiagent chemotherapy regimen involving cyclophosphamide, methotrexate and 5-fluorouracil or an anthracycline (doxorubicin) was used to treat BC women.	N=30 Mean age: 72.8 years (SD, 5.1 years) Race/ethnicity: Not disclosed (100%) Diagnosis: BC early stage I-IIIA with no metastasis.	Intelligence was measured using the four-subtest WASI. Both dimple and divided attention was measured using the DS, letter-number sequencing, and arithmetic subtest from the WAIS-3rd edition. The COWAT measures verbal fluency. Visuospatial was measured by the R-OCFT-DC and the FRT. Memory was measured by the RAVLT. Executive functioning was measured by the I/ES. Mood was measured by the BDI-II.	BC women with chemotherapy (N=30) scored significantly lower in the TMTB, TMTA, Letter-Number Sequencing subtest and committed more reversal errors on the I/ES task and demonstrated more perseverative errors on the WCST test compared with the HCs. Among disease-free BCSs for more than 10 years, the previous cancer treatment may further augment cognitive impairment associated with age-related brain change.

Table 3. *Component and Global Assessment of Study Quality by Using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies.*

First Author/year published	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropouts	Global Rating
Ahles, 2010	2	2	1	1	1	1	2
Biglia, 2012	2	2	1	1	1	1	2
Bower, 2013	2	2	1	1	1	1	1
Cerulla, 2017	2	2	1	1	1	1	2
Deprez, 2012	2	2	1	1	1	1	1
Jansen, 2011	2	2	1	2	1	1	2
Jung, 2017	2	2	1	1	1	1	2
Kesler, 2013	2	2	1	1	1	1	2
Kesler, 2016	2	2	1	1	1	1	2
Klemp, 2018	2	2	1	1	1	1	2

First Author/year published	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropouts	Global Rating
Miao, 2016	2	2	1	1	1	1	2
Menning, 2016	2	2	1	1	1	1	2
Ng, 2017	2	2	1	1	1	1	2
Piccirillo, 2015	2	2	1	1	1	1	2
Quesnel, 2009	2	2	1	1	1	1	2
Ramalho, 2017	2	2	1	1	1	1	2
Tao, 2016	2	2	1	1	1	1	2
Vardy, 2017	2	2	1	1	1	1	2
Xuan, 2017	2	2	1	1	1	1	2
Yamada, 2010	2	2	1	1	1	1	2

NOTE. Effective Public Health Practice Project Ratings: 1=strong, 2=moderate, 3=weak.
Abbreviation: NA, not applicable.

3. Results

Figure 1 illustrates the process of study identification and screening. A total of 816 articles were identified through the four health journal databases searches of PubMed, CINAHL, EMBASE, and Web of Science. After duplicate articles were removed, 638 titles and abstracts were screened. After removing 604 abstracts not meeting inclusion criteria, 35 articles resulted. After a full-text review, 15 articles were eliminated, leaving 20 articles qualified for inclusion for the synthesis of literature. Descriptions and findings from the included research articles are depicted in Table 2.

3.1. Quality of Evidence

Table 2 summarizes the methodologic quality evaluation used in this systematic review paper. The Effective Public Health Practice Project (EPHPP) was used to evaluate the study quality of the included research articles [21]. By using EPHPP criteria of high, moderate, and weak global quality ratings, all the studies received *moderate* global quality ratings [13, 15-20, 22-34]. No study received a weak global quality rating based on the EPHPP assessment tool [35]. The overall quality rating for the 20 reviewed articles was moderate.

3.2. Study Designs

Study designs used in the 20 sources included: one longitudinal study, eleven prospective studies, two case-control studies, two retrospective studies, and four cross-sectional studies. One longitudinal study explored the longitudinal changes in the brain white matter integrity after chemotherapy and cognitive functioning [33]. Among the eleven prospective studies, ten studies evaluated patient's cognitive function changes by comparing baseline data before chemotherapy to find associations between chemotherapy and cognitive impairment [15, 16, 19, 22, 24, 25, 27-30]. One of the eleven studies compared patients' cognitive function before and after standard chemotherapy that combined fluorouracil, epirubicin, and cyclophosphamide (FEC) with or without taxanes to identify the taxanes' role in CRCD [23]. Two case-control studies investigated the functional brain network changes of patient-perceived cognitive dysfunction after standard adjuvant chemotherapy [13, 26]. One retrospective study compared anthracycline-based and non-anthracycline-based chemotherapy to identify anthracycline regimens' neurotoxic effect in particular cognitive domains and brain network connections [17]. One retrospective study evaluated the long-term cognitive implications of chemotherapy among BCSs over 65 years old who received chemotherapy a decade ago [18]. Two cross-sectional studies investigated the brain's functional connectivity alteration after chemotherapy [20, 31]. One cross-sectional study investigated the chemotherapy-induced inflammation caused reduced hippocampal volume, which could be the basis for cognitive impairment [34]. One cross-sectional study explored the relationship between cytokine genetic variations and fatigue and cognitive decline [32].

3.3. Study Participant Characteristics

The number of study participants in each study ranged from 28 to 418 BCSs with a total of 1601 BCSs and 285 healthy controls. All the participants were 18 years and older, with a mean age around 50 years old, with most BCSs ranging from 18 years to 70 years of age [23]. The majority patient population had early-stage breast cancer and exposure to chemotherapy. Most of the studies included BCSs before, during, and after their chemotherapy, with a chemotherapy period ranging from seven days to more than ten years after chemotherapy treatment. A total of 618 BCSs were from the US, and 983 BCSs were from other countries. BCSs with pre-existing psychotic disorders, brain injury, or any neurological disorders were excluded from the subsequent clinical studies [17, 18, 22, 23].

3.4. Specific Cognitive Domains Affected by Chemotherapy

This review identified the specific cognitive domains affected by chemotherapy among BCSs: learning and memory, processing speed and executive function, concentration and attention, and verbal fluency [15, 28, 36]. *Memory, attention, and executive function* were particularly vulnerable to change due to chemotherapy [16]. By comparing with healthy controls, Miao et al. (2016) reported that chemotherapy could cause functional disconnection in the medial temporal lobe (MTL) of BCS, which is associated

with attention function [20]. Tao et al. (2016) found that chemotherapy-induced lower brain functional connectivity may lead to executive function impairment in BCS [31]. Yamada et al. (2010) conducted a retrospective study to explore the long-term cognitive implications of BCSs exposed to chemotherapy more than ten years ago. They found BCSs had lower scores which reached a significant level in the cognitive domains of working memory, divided attention, and executive functioning by comparing with noncancer healthy controls [9]. Research results showed chemotherapy has a particular adverse effect on a patient's *verbal fluency and verbal memory* [30]. A significant decline in the cognitive function subdomain of *attention* is reported after chemotherapy [22]. Significantly decreased short-term visual attention, memory, and executive functioning after chemotherapy are reported [23]. Overall, more than one cognitive domain may be affected by chemotherapy and, memory, attention, and executive functioning were affected most frequently.

3.5. Predictors of Chemotherapy-Induced Cognitive Dysfunction

This review identified specific predictors related to chemotherapy-related cognitive dysfunction. Along with chemotherapy, many other confounders such as anxiety and depression can contribute to patient-perceived cognitive dysfunction. Long-term symptoms of depression and anxiety are prevalent among BCSs [37]. Cognitive tests may be affected by high anxiety levels due to decreased attentional control [38]. Cancer-related post-traumatic stress also may impact cognitive functioning [39]. Klemp et al. (2018) explored specific predictors (patient's age, estradiol level, symptoms of depression, fatigue, neuropathy, body mass index, and exercise) of cognitive chemotherapy changes in BCSs. Results showed that symptoms of depression and fatigue were significantly increased between baseline (T1) and within 14-21 days of completing adjuvant chemotherapy (T3) with a return to baseline at eight years after chemotherapy (T4). Symptoms of depression and fatigue were identified as potential covariates of patient-perceived cognitive dysfunction. A significant relationship between body mass index (BMI) and patient-perceived cognitive dysfunction was found to be moderated by frequency of exercise [15]. Symptoms of anxiety, fatigue, depression, and distress were associated with worse physical and social cognitive functioning after chemotherapy [22, 25]. Ahles et al. (2010) found that age and pretreatment cognitive reserve are essential predictors of CRCD in the processing speed domain. The cognitive reserve decides innate and developed cognitive capacity and is defined as 3rd edition reading scores of Wide Range Achievement Test [28]. In total, pre-existing psychosocial issues such as anxiety, depression, fatigue, and emotional distress increase the chance of CRCD among BCSs. Older age and low pretreatment cognitive reserve are also predictors of CRCD. Jung et al. (2017) found that breast cancer stage was not associated with any cognitive status changes among women with early-stage localized breast cancer [24].

There was no association between patient-perceived cognitive dysfunction and objective cognitive decline [22, 40]. Biglia et al. (2012) runed a prospective study in breast cancer patients undergoing chemotherapy to explore if cognitive function changes can be recognized. They found that objective cognitive decline resulted independent of the patient's emotional status. Patient self-perceived cognitive dysfunction was found not to correlate with objective neuropsychological tests during the cognitive assessment [22]. Vardy et al. (2017) conducted a mechanical cohort study implementing comprehensive neuropsychological tests to characterize cognitive function while also exploring potential factors that may cause patient-perceived cognitive dysfunction by using laboratory and functional magnetic resonance imaging (fMRI) studies. Patient-perceived cognitive dysfunction was assessed by the questionnaire of Functional Assessment of Cancer Therapy-Cognition version 2 (FACT-Cog) and the Patient's Assessment of Own Functioning Inventory (PAFI). Objective neuropsychological tests include the Cambridge Neuropsychological Tests Automated Battery (CANTAB), the moderated Six Elements Tests (SET), and clinical neuropsychological tests. They found no association between patient-perceived cognitive dysfunction and objective neuropsychological scores [40].

Breast cancer patients often are treated with different chemotherapy regimens, and some chemotherapy regimens have a higher risk of causing CRCD. BCSs treated with doxorubicin plus cyclophosphamide with or without docetaxel had a four times higher risk of developing cognitive impairment than patients without chemotherapy [27]. Breast cancer patients treated with a regimen of fluorouracil, epirubicin, and cyclophosphamide (FEC) are reported to have altered cognitive functioning. BCS's cognitive performance was worse at the end of the cycles when treated with FEC plus taxane [23]. Kesler et al., 2016 conducted a cross-sectional study to compare anthracycline-based versus non-anthracycline-based chemotherapy effects on cognition changes in BCSs. Patients who received anthracycline-based chemotherapy had lower memory scores on an average two years after treatment compared to those who underwent non-anthracycline chemotherapy regimens or no chemotherapy [17]. CRCD is closely related to specific chemotherapy agents such as FEC, taxanes, and anthracyclines.

3.6. Underlying Mechanisms of Chemotherapy-Induced Cognitive Dysfunction

The underlying mechanisms of CRCD are very complicated, but chemotherapy's direct or indirect effects on brain structure and brain network functional connectivity may work as the major mechanism of CRCD. After chemotherapy, the structural and functional brain changes may lead to CRCD, especially the executive function impairment caused by the functional changes in the prefrontal cortex [31]. Chemotherapy-induced inflammation may contribute to hippocampal changes, which could be the

underlying of CRCD [34]. Chemotherapy decreased gray matter in the bilateral frontal area, temporal, thalamic, cerebellar, and cingulate regions resulting in CRCD [41]. Chemotherapy may also cause alterations in white matter in the brain in the long term with reductions in the brain structural volume [33, 42]. Askren et al. (2014) found that the frontoparietal executive network is particularly vulnerable in breast cancer patients affecting patient spatial learning function [43].

Research found that the functional disconnection in the medial temporal lobe (MTL) subsystem of the default mode network (DMN) may have an associated relationship with the attention function of BCSs after chemotherapy by using resting-state functional magnetic resonance imaging (rs-fMRI) [20]. The DMN connectivity change may be related to the chemotherapy caused effects of neurons or surrounding cells injury, neurotransmitter level alteration, oxidative damage, hormonal level changes, altered immune response, small blood vessel coagulation of the central nervous system, anemia, and genetic predispositions [20]. Tao et al. (2016) conducted research to choose the posterior cingulate cortex as the critical seed region to examine chemotherapy-induced alterations in the brain functional framework. The whole-brain functional connectivity was investigated by rs-fMRI, and abnormal brain functional connectivity was found mainly on the frontotemporal lobes [31]. Piccirillo et al. (2015) also found that women who had self-reported cognitive dysfunction after chemotherapy had disrupted resting-state functional connectivity after chemotherapy assessed by MRI [26]. Xuan et al. (2017) investigated the neural mechanism underlying chemotherapy-induced cognitive dysfunction in BCSs from a perspective of system-level network integrity. They found that CRCD is associated with large-scale functional brain networks abnormal organization that may contribute to memory impairment in BCSs [13].

Chemotherapy may cause neural inefficiency. Jung et al. (2017) conducted a prospective study to track the trajectory of neurocognitive function changes and patient-perceived cognitive impairment after chemotherapy and to explore possible contributory factors and overall symptom burden over twelve months in breast cancer patients. Adjuvant chemotherapy was found to be an independent predictive factor in a neurocognitive deficit of the executive network for BCSs. The use of an fMRI to measure patient-perceived cognitive dysfunction and objective neurocognitive task performance and executive network capacity showed cognitive dysfunction and neural inefficiency in executive network functioning usually persist over following months for patients who received adjuvant chemotherapy compared with those without chemotherapy and compared to healthy controls [24]. The brain-derived neurotrophic factor level changes were significant after chemotherapy. This change was related to patient self-perceived concentration deficit [16]. Some underlying reasons beyond a direct impact of chemotherapy may contribute to CRCD. Breast cancer women with high-expression variants of multiple cytokine genes are associated with greater levels of depression, fatigue, and memory complaints [32]. Besides, chemotherapy does not always predict neurological tests and patient cognitive complaints. It is possible that some distinct trajectories and differing contributory factors contributing to CRCD [44].

4. Discussion

The prevalence and extent of CRCD are recognized as a major risk for BCSs. It was not well understood due to the lack of ideal research design, varied definitions of cognitive dysfunction, and inadequate sensitive neuropsychological assessment tools been used in previous studies. Assessment of cognitive functioning is an important and necessary component of a comprehensive oncological care plan. More evidence of CRCD in BCSs is critical to assist health care professionals, and survivors in understanding cognitive impairments associated with cancer treatments so early interventions can be implemented to achieve optimal cognitive patient outcomes [45].

Although "cognitive decline" is reported in multiple studies focused on chemotherapy among BCS, the incidence rate and severity of cognitive dysfunction vary in different research studies [46]. More than one cognitive domain can be affected by chemotherapy, and memory, attention, and executive function were particularly vulnerable [16]. Jung et al. (2017) found changes in patients' neurocognitive executive network function were worse one year after chemotherapy than pre-adjuvant treatment and women without chemotherapy [24]. Often breast cancer patients report treatment-related cognitive deficits in several domains. However, cognitive deficits are mainly written in executive functioning, such as planning, problem-solving, and multitasking [47]. Research also reported cognitive dysfunction in disease-free BCSs related to previous cancer treatment ten years ago in the cognitive domains of working memory, divided attention, and executive functioning among BCSs [9].

Patient-perceived CRCD includes decreased memory, verbal fluency, concentration, executive function, and processing speed, but these findings are not always congruent with patient objective cognitive function tests [48]. Biglia, et al. (2012) conducted a small prospective study with 40 BCSs, and they found patient self-perceived cognitive dysfunction was not correlate with objective neuropsychological tests [22]. This result was confirmed by a more extensive study later. Vardy et al. (2017) conducted a mechanical cohort study with 154 BCSs, and they found no association between subjective patient-perceived cognitive dysfunction and objective neuropsychological scores [40]. A future longitudinal study with a large sample size needs to be done to clarify further the relationship between self-perceived cognitive impairment and object cognitive decline.

Other potential risk factors for CRCD include higher chemotherapy dose [49], cytostatic agent [50], lower cognitive reserve due to older age and lower educational level [28] and genetic factors such as high-expression variants of multiple cytokine genes have been identified as an

underlying reason for CRCD [32]. Various studies focused on CRCD also assessed the symptoms of depression, anxiety, and fatigue due to being identified as confounders of CRCD [23]. Aging and changes in menopausal status are identified as confounding factors for CRCD [51]. Several studies used breast cancer patient samples aged 70 years old and younger due to the possible age-related cognitive impairment and the association between underlying pathological changes such as dementia and Alzheimer's disease [23]. Menning et al. (2016) found no relationship between objective neuropsychological test scores and patient menopausal status and estrogen exposure [25].

A chemotherapy regimen of fluorouracil, epirubicin, and cyclophosphamide appears to alter the patient's cognitive function. The patient's cognitive function may worsen when taxane is added to the FEC regimen [23]. Anthracycline agents are used to treat breast cancer very commonly. Research shows that significant cognitive dysfunction occurs in women with breast cancer being treated exclusively with anthracycline-based agents [52]. Kesler et al. (2016 conducted a retrospective cross-sectional study with a small sample of 62 BCSs. They found that both anthracycline-based and non-anthracycline-based chemotherapy are associated with CRCD, but the degree of non-anthracycline agents is lesser [17]. Anthracyclines may disrupt metabolic resources significantly than other chemotherapy agents via increased mitochondrial dysfunction and exacerbate neurotoxic physiologic cascades [53, 54]. Anthracycline agents can produce reactive oxygen species which may result in oxidative stress associated with neurodegeneration [55, 56]. Anthracyclines can also cause neural progenitor cell damage and increase neuroinflammation [57].

The underlying mechanisms of CRCD are complex. They might include direct neurotoxicity, cytokine level alteration, changes of hormonal levels, and small cerebral vessel thrombosis caused by chemotherapy [58]. Several mechanisms to explain CRCD have been postulated. For example, changes in brain-derived neurotrophic factor (BDNF) levels were found to be related to patient-perceived concentration deficit in BCSs exposed to anthracycline-based and taxane-based chemotherapy [16]. There is evidence that BCSs may have pre-chemotherapy cognitive dysfunction associated with cancer-related factors [59]. Pretreatment cognitive problems may be a contributing factor for CRCD [60]. Functional connectivity disconnection has been found in patients with Alzheimer's disease, cognitive dysfunction, and schizophrenia [51]. The medial temporal lobe subsystem's lower functional connectivity can contribute to cognitive decline, especially attention deficit in BCSs after chemotherapy [20]. Inflammation caused by chemotherapy may contribute to hippocampal changes [34]. Decreased gray matter in bilateral frontal area, temporal, cerebellar, thalamic, and cingulate areas were also found after chemotherapy [41]. Chemotherapy may also cause alterations in white matter in the brain and reduce the brain structure volume [33, 42]. The structure alteration may reduce the brain network's functional specialization and cause modulated cognitive domains [61]. Some BCSs may be more sensitive to the standard chemotherapy treatment, resulting in alteration of functional connectivity in the brain networks controlling attention and executive function [26]. Chemotherapy caused neurotoxicity, pretreatment cognitive problems, brain structure alterations, and patient individual genetic predispositions may contribute to the underlying mechanism of CRCD.

4.1. Study Limitations

This integrative review's limitations and research implications include consideration that some of the chosen studies had a minimal sample size, which significantly limits study power for the examination of multiple variables and increases the risk of Type 1 and Type 2 errors. For example, four studies had a small sample of fewer than 50 participants [15, 20, 22, 26]. There were four cross-sectional studies that did not have a baseline cognitive function evaluation [20, 31, 32, 34]. Two retrospective studies [9, 17], two case-control studies [13, 26] and a mechanistic cohort study [40] also had no baseline cognitive function assessment. Some research did not implement objective cognitive assessments, with few identifying treatment approaches. Future randomized controlled, longitudinal studies are essential to evaluate the patient's baseline cognitive function before chemotherapy to investigate the attention deficit and executive function deficits caused by chemotherapy [20, 31]. Further research could also examine genetic modifiers of cognitive impairment. One limitation is the inconsistent definition of cognitive dysfunction that vary in measurement, ranging from a small number of cognitive domain scores to more than 20 test indices [26, 29]. There is no accordant number of abnormal test or cognitive domain scores required to classify cognitive dysfunction, which is vital for future investigations [25].

4.2. Clinical Implications

The clinical implications of this review include understanding the importance for health care professionals to 1) increase knowledge of CRCD due to the large BCS population has been affected; 2) initiate the early assessment of breast cancer patients' cognitive functioning who are receiving chemotherapy to decrease the potential risk factors; 3) understand the importance of starting early treatment and action to help manage CRCD due to the significant cognitive domains could be affected; and 4) continue to evaluate CRCD years after treatment has ended to implement effective interventions because CRCD can last more than a decade. Research showed that cognitive-behavioral therapy (CBT) and cognitive training methods might help with CRCD [62]. For example, breast cancer survivors' QOL and verbal memory performance can be increased through cognitive behavioral therapy and Memory and Attention Adaptation Training (MAAT) [63]. Some potential treatments based on small clinical trials also showed that metacognitive strategies, meditation, and Mindfulness-Based Stress Reduction (MBSR) might have positive effects on the symptoms of CRCD. A single group pre/post-test study with 14 BCSs showed that

metacognitive strategy training was associated positively with cognitive performance and neural connectivity in BCSs with CRCD [64]. A randomized controlled trial with 47 BCSs showed that the Tibetan Sound Meditation program might be an easy and accessible way that is associated with short-term increasing in objective and subjective cognitive function in BCSs [65]. Evidence also showed that mindfulness-based stress reduction (MBSR) has significant positive effects among BCSs on psychological and physical symptoms after chemotherapy. MBSR improves subjective cognitive performance and symptom clusters [66, 67]. Cognitive therapy protocols implemented after chemotherapy resulted in significantly improved verbal memory, attention, and processing speed [68].

5. Conclusions

Chemotherapy can cause acute and chronic cognitive dysfunction among BCSs. The major adverse effects of chemotherapy-related cognitive dysfunction include deficits in attention and executive functioning. Predictors associated with chemotherapy-related cognitive dysfunction include stress, fatigue, anxiety, depression, BMI, age, pretreatment cognitive reserve and specific chemotherapy agents. In the future, there is a need for more extensive, randomized controlled longitudinal trials and multicenter prospective studies targeting specific parameters and outcomes described in this review.

Abbreviations

AM, attentive matrices; DS, digit span; DSF, digit span forward; PWF, phonemic word fluency; SSIR, short story-immediate recall; SSDR: short story delayed recall; RPM, Raven's progressive matrices; CT, chemotherapy; BC, breast cancer; HC, health control; SD, standard deviation; CNS, central nervous system; VFT, verbal fluency test; CVLT-II, California Verbal Learning Test-II; LM, logical memory; PASAT, Paced Auditory Serial Addition Test; TMT, Trail Making Test; TMTA, Trail Making Test A; TMTB, Trail Making Test B; C-WIT, Color-Word Interference Test; GP, Grooved Pegboard; BCPT, breast cancer prevention trial; ST, sorting test; CPT, continuous performance test; BIT, Brief Intelligence Test; NART, National Adult Reading Test; STAI, State-Trait Anxiety Inventory; FEC, fluorouracil, epirubicin and cyclophosphamide; RBANS, Repeatable Battery of Adult Neuropsychological Status; GPT, Grooved Pegboard Test; ST, stroop test; SC, Stroop Color; SW, Stroop Word; SI, Stroop Interference; AFI, attentional function index; CES-D, the center for epidemiological studies-depression; SSAI-S, Spielberger State Anxiety Inventory; LFS, Lee Fatigue Scale; fMRI, functional magnetic resonance imaging; HVLT, Hopkins Verbal Learning Tests Revised; HVLT-R, Hopkins Verbal Learning Tests-Revised; MMQAS, Multifactorial Memory Questionnaire Ability Scale; MFSI, Multidimensional Fatigue Symptom Inventory; MQAS, Memory Questionnaire Ability Scale; PSQI, Pittsburgh Sleep Quality Index; SMQ, Squire Memory Questionnaire; WCST, Wisconsin Card Sorting Test; CTMT, comprehensive trail making test. D-KEFS, Delis-Kaplan Executive Function System Letter Fluency; COWA, controlled oral word association; BRIEF, behavioral rating inventory of executive function; CAD, clinical assessment of depression; HSCS, high sensitivity cognitive screen; QOL, quality of life; The FACT-C, functional assessment of cancer therapy-cognition; FACT-F, functional assessment of cancer therapy-fatigue; CANTAB, Cambridge Neuropsychological Test Automated Battery; SET, Six Elements Test; PAFI, Patient's Assessment of Own Functioning Inventory; GHQ, General Health Questionnaire; MDACI, MD Anderson Cancer Symptom Inventory; MoCA, Montreal Cognitive Assessment; CRF, cancer-related fatigue; HAMD, Hamilton depression rating scale; HARS, Hamilton anxiety rating scale; CFQ, cognitive failures questionnaire; GRC, global rating of cognition; CFT, complex figure test; RAVLT, Rey Auditory Verbal Learning Test; SDMT, symbol digit modalities test; DS, digit span; VMS, visual memory span; WMS-R, Wechsler Memory Scale -Revised; VFT, verbal fluency test; WALS -III, Wechsler Adult Intelligence Scale -III; MMSE, mini-mental state examination; WASI, Wechsler Abbreviated Scale of Intelligence; R-OCFT-DC, Rye-Osterrieth Complex Figure Test Delay Condition; FRT, facial recognition test; BDI, Beck Depression Inventory; EORTC-QOLQ, European Organization for Research and Treatment of Cancer QOL Questionnaire; HADS, Hospital Anxiety and Depression Scale; I/ES, Intradimensional /Extradimensional Shift; ECOG, Eastern Cooperative Oncology Group.

References

[1] Statistics, U. S. B. C. 2020; Available from: https://www.breastcancer.org.

[2] Breastcancer.org. *Chemotherapy*. 2019 [cited 2020 March 20]; Available from: https://www.breastcancer.org.

[3] Cancer.org. *Breast Cancer Facts & Figures 2019-2020*. 2019 [cited 2020 March 20]; Available from: https://www.cancer.org.

[4] Rodriguez Martin, B., et al., *Study of Chemotherapy-Induced Cognitive Impairment in Women with Breast Cancer.* Int J Environ Res Public Health, 2020. 17 (23).

[5] Wefel, J. S., et al., *International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer.* Lancet Oncol, 2011. 12 (7): p. 703-8.

[6] Ganz, P. A., *"Doctor, will the treatment you are recommending cause chemobrain?".* J Clin Oncol, 2012. 30 (3): p. 229-31.

[7] Pullens, M. J., J. De Vries, and J. A. Roukema, *Subjective cognitive dysfunction in breast cancer patients: a systematic review.* Psychooncology, 2010. 19 (11): p. 1127-38.

[8] Vardy, J., *Cognitive function in breast cancer survivors.* Cancer Treat Res, 2009. 151: p. 387-419.

[9] Yamada, T. H., et al., *Neuropsychological outcomes of older breast cancer survivors: cognitive features ten or more years after chemotherapy.* J Neuropsychiatry Clin Neurosci, 2010. 22 (1): p. 48-54.

[10] Jim, H. S., et al., *Cognitive functioning in breast cancer survivors: a controlled comparison.* Cancer, 2009. 115 (8): p. 1776-83.

[11] Jim, H. S., et al., *Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy.* J Clin Oncol, 2012. 30 (29): p. 3578-87.

[12] Wefel, J. S., et al., *Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer.* Cancer, 2010. 116 (14): p. 3348-56.

[13] Xuan, H., et al., *Altered network efficiency of functional brain networks in patients with breast cancer after chemotherapy.* Oncotarget, 2017. 8 (62): p. 105648-105661.

[14] Argyriou, A. A., et al., *Either called "chemobrain" or "chemofog," the long-term chemotherapy-induced cognitive decline in cancer survivors is real.* J Pain Symptom Manage, 2011. 41 (1): p. 126-39.

[15] Klemp, J. R., et al., *Cognitive functioning and quality of life following chemotherapy in pre- and peri-menopausal women with breast cancer.* Support Care Cancer, 2018. 26 (2): p. 575-583.

[16] Ng, T., et al., *Evaluation of plasma brain-derived neurotrophic factor levels and self-perceived cognitive impairment post-chemotherapy: a longitudinal study.* BMC Cancer, 2017. 17 (1): p. 867.

[17] Kesler, S. R. and D. W. Blayney, *Neurotoxic Effects of Anthracycline- vs Nonanthracycline-Based Chemotherapy on Cognition in Breast Cancer Survivors.* JAMA Oncol, 2016. 2 (2): p. 185-92.

[18] Murata, K., et al., *[Idiopathic thrombocytopenic purpura during chemotherapy for liver metastasis of rectal cancer].* Gan To Kagaku Ryoho, 2010. 37 (12): p. 2605-7.

[19] Vardy, J. L., et al., *A mechanistic cohort study evaluating cognitive impairment in women treated for breast cancer.* Brain Imaging Behav, 2017. (Please Delete this One)

[20] Miao, H., et al., *Functional connectivity change of brain default mode network in breast cancer patients after chemotherapy.* Neuroradiology, 2016. 58 (9): p. 921-8.

[21] Thomas, B. H., et al., *A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions.* Worldviews Evid Based Nurs, 2004. 1 (3): p. 176-84.

[22] Biglia, N., et al., *Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study.* Eur J Cancer Care (Engl), 2012. 21 (4): p. 485-92.

[23] Cerulla, N., et al., *Role of taxanes in chemotherapy-related cognitive impairment: A prospective longitudinal study.* Breast Cancer Res Treat, 2017. 164 (1): p. 179-187.

[24] Jung, M. S., et al., *Cognitive dysfunction and symptom burden in women treated for breast cancer: a prospective behavioral and fMRI analysis.* Brain Imaging Behav, 2017. 11 (1): p. 86-97.

[25] Menning, S., et al., *Cognitive Impairment in a Subset of Breast Cancer Patients After Systemic Therapy-Results From a Longitudinal Study.* J Pain Symptom Manage, 2016. 52 (4): p. 560-569 e1.

[26] Piccirillo, J. F., et al., *Cognitive impairment after chemotherapy related to atypical network architecture for executive control.* Oncology, 2015. 88 (6): p. 360-8.

[27] Ramalho, M., et al., *Cognitive impairment in the first year after breast cancer diagnosis: A prospective cohort study.* Breast, 2017. 32: p. 173-178.

[28] Ahles, T. A., et al., *Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve.* J Clin Oncol, 2010. 28 (29): p. 4434-40.

[29] Jansen, C. E., et al., *A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients.* Support Care Cancer, 2011. 19 (10): p. 1647-56.

[30] Quesnel, C., J. Savard, and H. Ivers, *Cognitive impairments associated with breast cancer treatments: results from a longitudinal study.* Breast Cancer Res Treat, 2009. 116 (1): p. 113-23.

[31] Tao, L., et al., *Impairment of the executive function in breast cancer patients receiving chemotherapy treatment: a functional MRI study.* Eur J Cancer Care (Engl), 2017. 26 (6).

[32] Bower, J. E., et al., *Cytokine genetic variations and fatigue among patients with breast cancer.* J Clin Oncol, 2013. 31 (13): p. 1656-61.

[33] Deprez, S., et al., *Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning.* J Clin Oncol, 2012. 30 (3): p. 274-81.

[34] Kesler, S., et al., *Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors.* Brain Behav Immun, 2013. 30 Suppl: p. S109-16.

[35] *Quality assessment tool for quantitative studies.*. 2008, Hamilton, ON: National Collaborating Centre for Methods and Tools.

[36] Jansen, C. E., et al., *A metaanalysis of studies of the effects of cancer chemotherapy on various domains of cognitive function.* Cancer, 2005. 104 (10): p. 2222-33.

[37] Maass, S. W., et al., *The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: A systematic review.* Maturitas, 2015. 82 (1): p. 100-8.

[38] Gass, C. S. and R. E. Curiel, *Test anxiety in relation to measures of cognitive and intellectual functioning.* Arch Clin Neuropsychol, 2011. 26 (5): p. 396-404.

[39] Hermelink, K., et al., *Elucidating pretreatment cognitive impairment in breast cancer patients: the impact of cancer-related post-traumatic stress.* J Natl Cancer Inst, 2015. 107 (7).

[40] Vardy, J. L., et al., *A mechanistic cohort study evaluating cognitive impairment in women treated for breast cancer.* Brain Imaging Behav, 2017. 13 (1): p. 15-26. (Keep this one).

[41] Deprez, S., et al., *Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients.* Hum Brain Mapp, 2011. 32 (3): p. 480-93.

[42] De Ruiter, M. B., et al., *Late effects of high-dose adjuvant chemotherapy on white and gray matter in breast cancer survivors: converging results from multimodal magnetic resonance imaging.* Hum Brain Mapp, 2012. 33 (12): p. 2971-83.

[43] Askren, M. K., et al., *Neuromarkers of fatigue and cognitive complaints following chemotherapy for breast cancer: a prospective fMRI investigation.* Breast Cancer Res Treat, 2014. 147 (2): p. 445-55.

[44] Janelsins, M. C., et al., *Prevalence, mechanisms, and management of cancer-related cognitive impairment.* Int Rev Psychiatry, 2014. 26 (1): p. 102-13.

[45] Pendergrass, J. C., S. D. Targum, and J. E. Harrison, *Cognitive Impairment Associated with Cancer: A Brief Review.* Innov Clin Neurosci, 2018. 15 (1-2): p. 36-44.

[46] Wefel, J. S., et al., *Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults.* CA Cancer J Clin, 2015. 65 (2): p. 123-38.

[47] Allen, B. J., S. A. Reid-Arndt, and T. Rolan, *Neuropsychological functioning in a young adult case of schizencephaly.* Clin Neuropsychol, 2010. 24 (5): p. 827-40.

[48] Hutchinson, A. D., et al., *Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review.* Cancer Treat Rev, 2012. 38 (7): p. 926-34.

[49] Collins, B., et al., *Cognitive effects of chemotherapy in breast cancer patients: a dose-response study.* Psychooncology, 2013. 22 (7): p. 1517-27.

[50] Seigers, R. and J. E. Fardell, *Neurobiological basis of chemotherapy-induced cognitive impairment: a review of rodent research.* Neurosci Biobehav Rev, 2011. 35 (3): p. 729-41.

[51] Binnewijzend, M. A., et al., *Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment.* Neurobiol Aging, 2012. 33 (9): p. 2018-28.

[52] McDonald, B. C., et al., *Alterations in brain activation during working memory processing associated with breast cancer and treatment: a prospective functional magnetic resonance imaging study.* J Clin Oncol, 2012. 30 (20): p. 2500-8.

[53] Mordente, A., et al., *Anthracyclines and mitochondria.* Adv Exp Med Biol, 2012. 942: p. 385-419.

[54] Sanoff, H. K., et al., *Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer.* J Natl Cancer Inst, 2014. 106 (4): p. dju057.

[55] Joshi, G., et al., *Alterations in brain antioxidant enzymes and redox proteomic identification of oxidized brain proteins induced by the anti-cancer drug adriamycin: implications for oxidative stress-mediated chemobrain.* Neuroscience, 2010. 166 (3): p. 796-807.

[56] Niedzielska, E., et al., *Oxidative Stress in Neurodegenerative Diseases.* Mol Neurobiol, 2016. 53 (6): p. 4094-4125.

[57] Janelsins, M. C., et al., *Differential expression of cytokines in breast cancer patients receiving different chemotherapies: implications for cognitive impairment research.* Support Care Cancer, 2012. 20 (4): p. 831-9.

[58] Ahles, T. A. and A. J. Saykin, *Candidate mechanisms for chemotherapy-induced cognitive changes.* Nat Rev Cancer, 2007. 7 (3): p. 192-201.

[59] Ando-Tanabe, N., et al., *Cognitive function in women with breast cancer receiving adjuvant chemotherapy and healthy controls.* Breast Cancer, 2014. 21 (4): p. 453-62.

[60] Berman, M. G., et al., *Pretreatment worry and neurocognitive responses in women with breast cancer.* Health Psychol, 2014. 33 (3): p. 222-31.

[61] Anticevic, A., et al., *The role of default network deactivation in cognition and disease.* Trends Cogn Sci, 2012. 16 (12): p. 584-92.

[62] Sleight, A., *Coping with cancer-related cognitive dysfunction: a scoping review of the literature.* Disabil Rehabil, 2016. 38 (4): p. 400-8.

[63] Ferguson, R. J., et al., *Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial.* Psychooncology, 2012. 21 (2): p. 176-86.

[64] Wolf, T. J., et al., *The Feasibility of Using Metacognitive Strategy Training to Improve Cognitive Performance and Neural Connectivity in Women with Chemotherapy-Induced Cognitive Impairment.* Oncology, 2016. 91 (3): p. 143-52.

[65] Milbury, K., et al., *Tibetan sound meditation for cognitive dysfunction: results of a randomized controlled pilot trial.* Psychooncology, 2013. 22 (10): p. 2354-63.

[66] Lengacher, C. A., et al., *Mindfulness based stress reduction in post-treatment breast cancer patients: an examination of symptoms and symptom clusters.* J Behav Med, 2012. 35 (1): p. 86-94.

[67] Lengacher, C. A., et al., *Moderating Effects of Genetic Polymorphisms on Improvements in Cognitive Impairment in Breast Cancer Survivors Participating in a 6-Week Mindfulness-Based Stress Reduction Program.* Biol Res Nurs, 2015. 17 (4): p. 393-404.

[68] Morean, D. F., L. O' Dwyer, and L. R. Cherney, *Therapies for Cognitive Deficits Associated With Chemotherapy for Breast Cancer: A Systematic Review of Objective Outcomes.* Arch Phys Med Rehabil, 2015. 96 (10): p. 1880-97.