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REVIEW

Systematic review of cognitive sequelae of non-central nervous system cancer and cancer therapy

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Abstract

Purpose The aim of this review is to provide an updated overview of chemotherapy-related cognitive impairment (CRCI) in patients with cancer outside central nervous system (CNS), its incidence and prevalence, the cognitive pattern in neuropsychological studies, neuroimaging findings, and the relationship between chemobrain and aging. Methodological limitations of studies are also discussed.

Methods This review was guided by the PRISMA statement. The MEDLINE and Scopus databases were employed to search articles about CRCI in non-CNS cancer patients published from January 2004 to September 2019. Two types of research were reviewed: prospective studies addressing the effects of chemotherapy on cognition and systematic reviews about factors related with CRCI, also as neuroimaging findings and current available treatments.

Results Fifty-nine studies meeting the criteria were analyzed: 47 were longitudinal studies on cancer and cognition and 12 were reviews on risk factors, neuroimaging, and treatment. The majority of studies find cognitive impairment in patients with cancer treated with chemotherapy. The body of the literature on breast cancer is the most abundant, but there are also studies on colorectal, testicular, and lung cancer. Neuroimaging studies show changes in structure and activation in patients undergoing chemotherapy. Non-pharmacological treatment is effective for improving cognition and quality of life.

Conclusions The occurrence of CRCI during the course of treatment in people with different types of cancer is frequent. Some risk factors have been identified, but CRCI is a complex phenomenon, with mediating factors related to cancer and treatment and moderating factors related with lifestyle and health.

Implications for Cancer Survivors This review highlights the importance of recognizing that this cognitive dysfunction is frequent, mild to moderate in nature but with great impact on quality of life.

Keywords Cancer · Chemobrain · Chemotherapy · Cognitive impairment · Neuropsychology

Introduction

Nowadays, the early detection of cancer, the availability of interventions, and efficacy of treatment have led to increased survival rates. However, treatments have also adverse effects; some of them can be long lasting and/or late onset. Therefore, the patient with cancer will live with long-term consequences. Recently, the phenomenon of chemobrain (or cancer and chemotherapy-related cognitive impairment—CRCI) has received considerable attention. The aim of this paper is to review the existing literature on cognitive impairment in people with cancer outside central nervous system (CNS) focusing on its characteristics and neuropsychological pattern, trajectory, causes, and treatment.

Chemobrain: general considerations

Chemobrain or chemofog is defined as a worsening in cognitive function related to cancer treatment, mild to moderate in nature but with great impact on quality of life that can also hamper the survivors' ability to return to work [1, 2].

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Forgetfulness, distractibility, difficulty with focusing attention and with multitasking, and the tip-of-the-tongue phenomenon [3] are frequent complaints. It is detected with neuropsychological tests and it can be assumed erroneously as associated to affective disorders (anxiety, depression) secondary to a diagnosis of cancer [4]. Nowadays, there is a lack of consensus regarding diagnostic criteria for CRCI [5].

Most studies on cognition and cancer investigate women with breast cancer treated with chemotherapy, but recently patients with colorectal [6, 7], testicular [8], and lung [9] cancer have also been investigated. These studies also find cognitive changes related to treatment and now research is focusing on risk factors that predispose patients to CRCI [10].

First studies on chemobrain are from 1980 [11], but research on cognition and cancer starts in 2004 with the first longitudinal study. In this study, women with breast cancer were assessed before the start of chemotherapy and after treatment and finding shows that cognitive impairment was detected before chemotherapy in a 33% of the sample. This finding is also found in other studies [12–15] and currently it is considered that between 20 and 30% of patients have cognitive impairment before any systemic therapy. It is hypothesized that cancer itself could induce biologic mechanisms that would promote this early cognitive impairment in a subgroup of patients, but risk factors are yet to be identified [16].

The term chemobrain is commonly used to provide information for patients, but in medical literature, it is referred as cancer-related cognitive impairment (CRCI). From a pharmacotoxicology perspective that link chemotherapy with cognitive decline, research has progressed to a more complex conceptualization, studying CRCI as a phenomenon with a complex interaction of factors not mutually exclusive, with mediating factors related with cancer and treatment and moderating factors related with health and lifestyle [17].

Methods

Search strategy

This systematic review adhered to the PRISMA statement for reporting systematic reviews [18]. The MEDLINE and Scopus databases were employed to search articles about the effects of chemotherapy on cognitive functions in non-CNS cancer patients published from January 2004 to September 2019. Two types of research were reviewed. First, prospective studies addressing the effects of chemotherapy on cognition was reviewed with the aim to provide an overview of the occurrence and characteristics of CRCI. Second, and to give a general outlook of CRCI, systematic reviews about factors related with CRCI, also as neuroimaging findings and current available treatments were reviewed. The following key search terms were used: "cancer," "chemotherapy," "cognitive impairment," "neuropsychological effect," and "longitudinal study" for longitudinal studies on CRCI and "cancer," "chemotherapy," "neuroimaging," "treatment," "risk factors," and "systematic review" for reviews. The search was limited to studies published in English language. Further manual searches of the reference lists of the relevant studies and reviews were undertaken by author NC.

All titles obtained from the search strategy were reviewed by the first author (NC). Full-text copies of the relevant articles were obtained and reviewed by the first author (NC). Any disagreement regarding study eligibility was resolved by consensus. Studies were eligible if (i) original longitudinal research on cognition and cancer was reported and (ii) they were reviews or systematic reviews. Data abstraction was completed by the first author.

Animal studies; studies on hematological malignancies, metastatic cancer, and pediatric oncology; and studies with patients treated only with hormonal therapy were excluded. Studies with only subjective cognitive assessment also were excluded.

Selection strategy

Screening of 362 citations identified a total of 186 potentially relevant papers; the full texts of which were retrieved. Fifty-nine studies met the inclusion criteria for final review: 47 were longitudinal studies on cancer and cognition and 12 were reviews on risk factors, neuroimaging, and treatment. A flow chart detailing the identification of studies is provided in Fig. 1.

Thirty-nine of the 47 longitudinal studies included in the review investigated breast cancer patients. Four studies investigated colorectal patients, three investigated testicular patients, and one investigated lung cancer patients. For longitudinal studies, the following data were retrieved: (i) first author and year of publication, (ii) type of cancer, (iii) whether cognitive impairment was found or not, (iv) assessment schedule, (v) number of patients on chemotherapy, (vi) use of a control group, (vii) method to control practice effects in neuropsychological assessment, (viii) definition of cognitive impairment, (ix) definition of cognitive decline, and (x) proportion of cognitive impairment found in chemotherapy group. These characteristics are listed in Table 1.

Results

Incidence and prevalence of CRCI

The 1-year incidence of breast cancer varies considerably between studies [62]. Some authors suggest it is between 17 and 75% of treated women [63], but these numbers are from initial studies, most of them are cross-sectional and also based on the

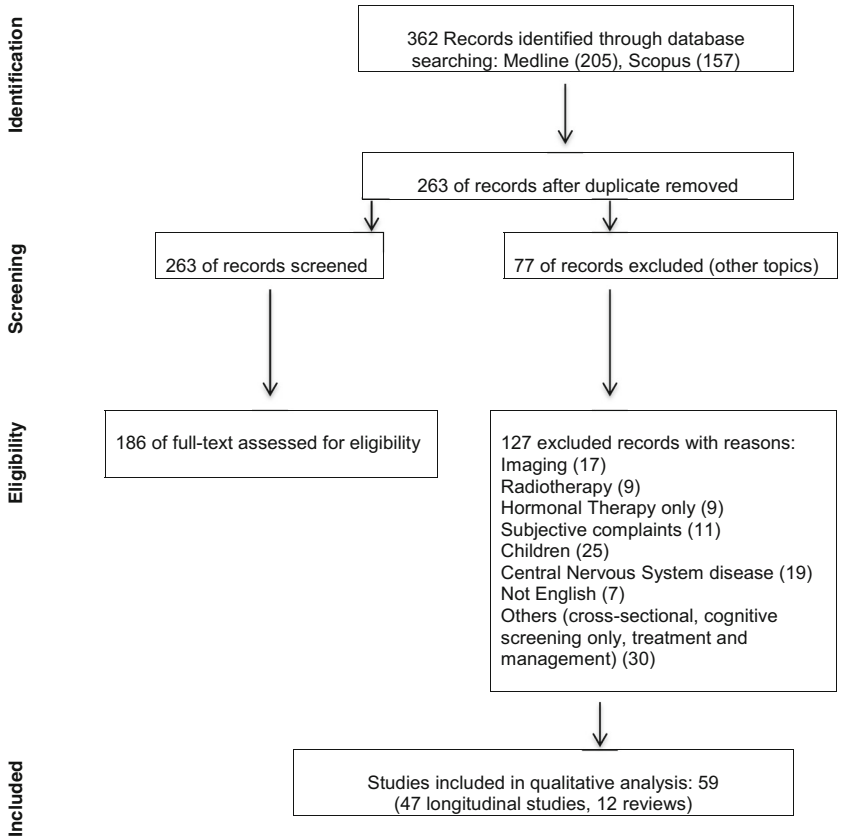

Fig. 1 The PRISMA flow chart for the study selection process

patients' subjective complaints. When objective assessment is included, the percentage is about 33% [62]. In the case of prevalence, longitudinal studies reveal that between 65 and 75% of patients show worsening of cognitive functioning when chemotherapy is finished [64–66] and about a 35% will continue with cognitive impairment compared with baseline before treatment or even years after treatment is finished [67, 68]. The incidence and prevalence of CRCI in other type of cancer are yet to be determined.

Neuropsychological profile

Recent longitudinal studies show that CRCI is more diffuse rather than localized in one hemisphere [69, 70], with a frontal subcortical profile [71]; with impairment in attention, memory, and executive functions; and also with slower speed of information processing. Other functions as language or visuospatial and visuoconstructional ability are preserved during treatment with chemotherapy for breast cancer [66, 72]. This neuropsychological profile is consistent with subjective complaints, such as diminished concentration and memory and difficulty with multitasking [73]. In other type of cancer, subjective complaints are very similar to the ones reported in breast cancer patients [74], although the neuropsychological profile is different. Verbal memory worsening has been found in patients with colorectal cancer treated with chemotherapy [6]. Patients with small cell lung cancer showed impairment in phonemic fluency, information processing, working memory, and visuospatial abilities after treatment with chemotherapy and when compared to controls [9]. That is, the neuropsychological pattern is slightly different depending on the type of cancer and treatment.

Trajectory of CRCI

The appearance of CRCI is variable throughout the course of the disease and treatment, but it is more frequent when chemotherapy cycles end [75]. This is related with findings that suggest that CRCI is dose dependent [76].

Currently, it is considered that CRCI ameliorates gradually between 1 and 2 years after treatment [10]. However, a subgroup of patients can experience delayed cognitive impairment, not present when chemotherapy was finished [37].

Etiology and risk factors for CRCI

CRCI is presumed to be multifactorial. Direct neurotoxic injury of some chemotherapeutic agents that readily able to cross the blood–brain barrier (BBB) and indirect injury like the releasing of proinflammatory cytokines, telomere shortening, changes in BBB integrity (that would increase its permeability), cardiotoxicity, or other secondary effects of

Table 1 Summary of longitudinal studies about cancer and cognition included

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
Wefel et al. (2004) [19]	BC	Yes	Prechemotherapy (T1) 3 weeks Postchemotherapy (T2) 1-year Postchemotherapy (T3)	18	No	Yes Alternate forms when possible	*z* scores ≤1.5 in more than 1 test ≤2.0 in a single test	*z* scores ≤1.5 in more than 1 test ≤2.0 in a single test	T1: 33% cognitively impaired T2: 61% cognitively impaired T3: of decliners at T2, 45% remain stable, 45% improve, and 10% mixed results
Shilling et al. (2005) [20]	BC	Yes	CT group: - Prechemotherapy (T1) - Postchemotherapy (T2) Control group: - Baseline (T1) - 6 months (T2)	50	*N* = 43 Healthy convenience sample	Yes Reliable Change Index corrected for practice effects (RCIpe)	NR	Meaningful cognitive decline: decline in 2 or more tests (of 14)	At T2: - Meaningful decline: 34% BC and 18.6% controls. - Reliable improving at least in one measure: 53% BC and 75% controls
Bender et al. (2006) [21]	BC	Yes	CT and CT+HT groups: - Prechemotherapy (T1) - 1 week Postchemotherapy (T2) - 1 year from T2 (T3) Ductal carcinoma in situ (DCIs) group: - Postsurgery (T1) - A comparable time to CT groups (T2) - 1 year from T2 (T3)	19 CT 15 CT + HT	*N* = 12 DCIs	No	NR	Statistically significant differences	Women receiving CT and tamoxifen: decline in verbal and visual memory Women receiving CT: decline in verbal memory Women without CT: improvement at final assessment due to practice effect
Hurria et al. (2006) [22]	BC	Yes	Prechemotherapy (T1) 6 months postchemotherapy (T2)	28	No	NR (not reported)	Scores < 2SD below the norm in 2 or more tests	1 SD decline from pre- to posttesting in 2 or more tests across 2 or more neuropsychological domains	T1: 11% cognitively impaired T2: 29% cognitively impaired At T2: - 50% no change - 39% decline - 11% improved
Jenkins et al. (2006) [23]	BC	No	CT group: - Prechemotherapy (T1) - 4 weeks postchemotherapy (T2) - 18 months from T1 (T3) Control group: - Baseline (T1) - 6 months (T2) - 18 months from T1 (T3)	85 CT 45 RT/HT	*N* = 49 Healthy convenience sample	Yes RCIpe	NR	- Decline if lower scores in 2 or more measures - Improve if better scores in 2 or more measures	Reliable decline on multiple tests: At T2 - CT: 20% - Non-CT: 26% - Controls: 18% Similar proportions of cognitive decline in the three study groups Similar improvement in 2 or more measures in T2. At T3 - CT: 18% - Non-CT: 14% - Controls: 11% More improvement in T3 in the chemotherapy group
	BC	Yes	CT group:		*N* = 60	Yes			Deterioration over time: 25% CTC vs 6.7% controls

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
Schagen et al. (2006) [24]			- Prechemotherapy (T1) - 6 months from Postchemotherapy (T2) Control group: - Baseline (T1) - 6 months from T1 (T2)	28 high-dose CT (CTC) 39 standard-dose CT (FEC) 57 RT	Healthy convenience sample	RCIpe	Scores 2 SD below the mean of the healthy control group at least in 3 of the 24 tests indices	Statistically significant decline in performance on at least 4 of 24 tests	Women on CTC regimen decline cognitive performance compared to healthy subjects (statistically significant)
Hermelink et al. (2007) [13]	BC	No	- Prechemotherapy (T1) - Towards the end of CT (5 months from baseline; T2)	101	No	Yes RCIpe	- Mild cognitive impairment: > 1 test result ≤ 1.5 SD - Moderate cognitive impairment: in addition, ≥ 1 test result ≤ 2SD	NR	T1: scores below the mean in 5 of 12 tests ($^1/_3$ show cognitive impairment before chemotherapy): - 53% mild cognitive impairment - 32% moderate cognitive impairment T2: ¼ improve, ¼ worsens No consistent pattern of affected cognitive domains
Ruzich et al. (2007) [25]	BC	Yes	Prechemotherapy (T1) 3 months (T2) 6 months (T3) 12 months (T4)	35	No	No	1 SD or more below the mean of the published normative data for each test	Statistically significant differences	T1: half of the patients: mild impairment in 2 or more neuropsychological tests T3: impairment in short-term verbal memory and verbal learning Stability or even improvement of the other domains attributed to practice effects
Hermelink et al. (2008) [26]	BC	No	- Prechemotherapy (T1) - Towards the end of CT (5 months from baseline; T2) - 1 year from baseline (T3)	101	No	No	NR	NR	Improvement through assessments
Jansen et al. (2008) [27]	BC	Yes	- Prechemotherapy (T1) - Postchemotherapy (T2)	30	No	Yes Alternate forms when possible	< 1.5 SD below published norms on 2 or more tests Or 2 SD on one test	Decline: decrease in 1 or more SD on two or more tests	T1: 13% cognitively impaired Decline as a group in visuospatial skill and total cognitive scores Improvement in executive function (Stroop test)
Stewart et al. (2008) [28]	BC	Yes	- Prechemotherapy (T1) - Postchemotherapy (T2)	61	$N = 51$ Hormonal therapy (HT)	Yes Standard regression-based (SRB) for each score for each subject	NR	- Reliable overall cognitive decline: if 2 or more SRB scores − 2.0 or less - Improvement: ≥ 2SD above expected in 2 or more cognitive measures	Reliable decline: 31% CT group vs 12% HT group
Collins et al. (2009) [29]	BC	Yes	CT group: - Prechemotherapy (T1) - 1 month postchemotherapy (T2) - 1 year from T2 (T3) Control group:	53	$N = 40$ HT	Yes SRB for each score	NR	- Reliable overall cognitive decline: if 2 or more SRB scores − 2.0 or less - Reliable cognitive improvement: 2 or more SRB scores of + 2 or greater	T1: - CT patients: better performance in 4 cognitive measures (assessing memory) T2: - CT patients worsen - 8% improvement in both groups -T3: reliable decline: 10% CT patients vs 11% HT patients reliable improvement: 5% CT vs 11% HT

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
			- Tested at comparable intervals						
Mehlsen et al. (2009) [30]	BC	No	CT group: - Prechemotherapy (T1) - Postchemotherapy (T2) Cardiac patients: - 4 days after hospitalization (T1) - 3 months (T2) Healthy patients: - Baseline (T1) - At 12–16 weeks (T2)	34	$N = 12$ Healthy $N = 12$ Cardiac patients	Yes RCIpe	NR	- In separate test: reduction in test score at follow-up exceeding RCIpe - General cognitive decline: decline on 3 or more out of the 21 cognitive measures	- Decline on 2 or more cognitive measures: 29% CT patients vs 25% cardiac patients vs 17% healthy controls - Improvement in 3 or more cognitive measures: 24% cancer patients vs 33% cardiac patients vs 25% healthy controls
Quesnel et al. (2009) [31]	BC	Yes	CT group: - Prechemotherapy (T1) - Postchemotherapy (T2) - 3 months from T2 (T3) RT group: - Previous to radiotherapy (T1) - Posterior to radiotherapy (T2) - 3 months from T2 (T3) Control group: - Baseline	41	$N = 40$ RT $N = 45$ Healthy	Yes Alternate forms in some tests	NR	NR	CT: decline in verbal fluency CT and RT: decline in verbal memory
Vearncombe et al. (2009) [32]	BC	Yes	CT group: - Prechemotherapy (T1) - 1 month after completing CT (T2) Control group: - At similar time points	138	$N = 21$ HT Radiotherapy (RT) and/or surgery only	Yes RCIpe	Cutoff to determine impairment en each cognitive measure: 1.96 SD	- Impairment on specific cognitive test: significant decline using RCIpe - Multiple test decline: significant decline on ≥ 2 cognitive tests	T2: - CT patients: significant decline (multiple test decline) found in 16.9% of this group
Ahles et al. (2010) [33]	BC	Yes	CT group: - Prechemotherapy (T1) - 1, 6, and 18 months postchemotherapy Non-CT patients and healthy controls: assessed at matched intervals	60	$N = 45$ Healthy $N = 72$ Non-CT	No	NR	Statistically significant differences	CT group: fails to improve at 1 month, improve during last two follow-up assessments CT group: lower performance on processing speed in older patients with lower baseline cognitive reserve Healthy controls and no-CT group: improved over time

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
Biglia et al. (2010) [34]	BCs	No	- After surgery before treatment (T1) - Postchemotherapy or at least 6 months of endocrine therapy (T2) - After a year of T1 (T3)	35 CT	No	No	NR	Statistically significant differences	Improvement in cognitive tests
Debess et al. (2010) [35]	BC	No	CT and tamoxifen group: - Before start of adjuvant treatment (T1) - After 6 months of T1 (T2) Healthy group: - Baseline (T1) - 6 months from T1 (T2)	120 (CT or tamoxifen)	*N* = 208 Healthy	Yes Alternate forms in some tests	NR	NR (% of decline or improvement in 2 or more tests reported)	Change not found
Tager et al. (2010) [36]	BC	No	CT group: - Prechemotherapy (T1) - Within a month completing chemotherapy (T2) - 6 months from T2 (T3) HT group: - Postsurgery before treatment (RT, TH) (T1) - 6 months after T1 (T2) - 6 months from T2 (T3)	30 CT	*N* = 31 HT	No	NR	NR	Non-significant decline in motor function over time in CT group vs improvement in control group General improvement in language and visuospatial ability
Wefel et al. (2010) [37]	BC	Yes	- Prechemotherapy (T1) - Postchemotherapy (T2) - 1 year postchemotherapy (T3)	42 CT	No	Yes RCIpe	Same as Wefel 2004	Same as Wefel 2004	T1: 24%cognitively impaired T2: 65% cognitively impaired T3: 61% cognitively impaired
Jansen et al. (2011) [38]	BC	Yes	- Prechemotherapy (T1) - 1 week postchemotherapy (T2)	67 CT	No	No	Same as Jansen 2008	Same as Jansen 2008	T1: 23% cognitively impaired T2: 52% cognitively impaired T3: improvement.

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
			- 6 months postchemotherapy (T3)						
Skaali et al. (2011) [39]	TC	No	- Prechemotherapy (T1) - Follow-up (a median of 12 months after end of treatment) (T2)	122	Yes $N = 31$ (no chemotherapy) $N = 38$ (one cycle of chemotherapy) $N = 53$ (two or more cycles of chemotherapy)	Yes Alternate forms	Average of z scores of change	Individual "decline": decline on ≥ 10% of test measure	No negative effect of systemic chemotherapy at 1-year follow-up
Biglia et al. (2012) [40]	BC	Yes	- Prechemotherapy (T1) - Postchemotherapy (T2) - Emotional evaluation before and after 1, 2, and 3 months from CT	40 CT	No	No	NR	Statistically significant differences	T1: impairment not found T2: decline in global cognitive function (MMSE) and visual selective attention Improvement in processing speed attributed to practice effects
Hedayati et al. (2012) [41]	BC	Yes	Experimental group: - Before diagnosis (T1) - After surgery and before adjuvant treatment (T2) - 6 months after T2 (T3) - 3 months after T3 (T4) Healthy group: assessed at same intervals (after enrollment before diagnosis -T1- and 2 -T2-, 8 -T3-, and 11 -T4- months after T1)	18 CT 45 HT 14 no adjuvant treatment	$N = 69$ Healthy	Yes Alternate forms in some test	NR	Statistically significant differences	All groups improve significantly overtime in processing speed and attention Attributed to practice effects CT patients do not improve in memory. It is considered that the expected practice effect is not found
Andreis et al. (2013) [42]	CC	No	- Prechemotherapy (T1) - Postchemotherapy (T2) - After 6 months (T3)	57	No	No	Considered using the international standardized cutoff	Statistically significant differences	Improvement in T3 scores vs T0 in statistical analysis in verbal memory and information processing speed
Collins et al. (2013) [43]	BC	Yes	- Prechemotherapy (T1) - Following each chemotherapy cycle	60 CT	$N = 60$ Healthy matched on age and education	Yes Use of control group to calculate SRB and	2 standard scores ≤ 2 out of a total of 17 cognitive measures	NR	WM and processing speed: the most sensitive to CT BC with CT did not benefit from practice effect to the same extent as control group. That it is considered an indication of cognitive dysfunction

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
			and at yoked intervals in healthy controls (T2, T3, T4, T5, T6, T7)			alternate forms in some test			
Ando-Tanabe et al. (2014) [44]	BC	No	CT group: - Prechemotherapy (T1) - Postchemotherapy (T2) Controls assessed at matched intervals.	18 CT	$N = 20$ Healthy	No	NR	Statistically significant differences	Change not found
Collins et al. (2014) [45]	BC	Yes	Same as Collins et al. (2013) plus long-term follow-up (i.e., 1 year -T8-)	56 CT	$N = 56$ Healthy	Yes same as Collins et al. (2013)	NR	Decline: SRB score of ≤ -2 on 3 or more of the 19 cognitive measures Improvement: SRB score of $\geq +2$ on 3 or more of the 19 cognitive measures	Prechemotherapy postchemotherapy: 48% BC decline vs 9% controls Prechemotherapy-1 year Postchemotherapy: 22% BC vs 6% controls Postchemotherapy-1 year Postchemotherapy: proportion of improvement in BC: 30% vs 17% improvement in controls
Cruzado et al. (2014) [6]	CC	Yes	- Prechemotherapy (T1) - Postchemotherapy (T2) - After 6-month follow-up (T3)	81	No	No	z scores ≤ 1.5 in more than 1 test ≤ 2.0 in a single test	Statistically significant differences	T1: 37% cognitively impaired (processing speed and psychomotor executive function) T2: 56% cognitively impaired (verbal memory) T3: 54% improve 33% worsens at least in 1 test
Lepage et al. (2014) [46]	BC	Yes	CT group: prechemotherapy (T1) 1 month postchemotherapy (T2) 1 year postchemotherapy (T3) Control group: similar intervals	19	$N = 19$	Yes Raw patient data converted to standardized scores based on means and SD of the control group	NR	Statistically significant differences	T2: worsening on processing speed (statistically significant) T3: improving on processing speed (ns) Working memory, verbal and visual memory: worsening over time (ns)
Wefel et al. (2014) [47]	TC	Yes	- Prechemotherapy (T1) - 1 week postchemotherapy (3 months later in the comparison group) (T2) - 12 months after the baseline evaluation (T3)	55 Low exposure and high exposure	Yes $N = 14$ Non-seminomatous germ cell tumors not receiving CT (surveillance group)	Yes Alternate forms	NR	Cognitive decline: SRB score of < 2.0 Overall cognitive decline: declining on > 2 tests	T2: overall cognitive decline - Surveillance group: 0% - Low exposure group: 17% - High exposure group: 29% T3: low and high exposure groups: greater rates of decline (vs surveillance group) in dominant hand fine motor dexterity - High exposure: greater decline on psychomotor speed
Simó et al. (2015) [9]	LC	Yes	Small cell lung cancer (SCLC): - Before CT	22	Yes	No	NR	Statistically significant differences	SCLC: decrease in verbal fluency over time

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
			- 3 months after treatment Non-small cell lung cancer (NSCLC): - Before prophylactic cranial irradiation (PCI) - 3 months after treatment - Control group assessed at a comparable time to treatment		*N* = 21 age and education-matched healthy adults *N* = 13 NSCLC				PCI-induced changes are mainly responsible for the brain structure and neuropsychological findings observed PCI seems to expand the cognitive and gray matter structural deficits already observed after chemotherapy in patients with SCLC, but adding brain-specific white matter damage exclusively in the corpus callosum at 3 months follow-up
Vardy et al. (2015) [7]	CC	No	- Prechemotherapy (T1) - 6 months (T2) - 12 months (T3) - 24 months (T4)	289 patients with localized CRC (173 received CT)	Yes *N* = 73 Limited metastatic/recurrent CRC *N* = 72 Healthy	Yes SRB adjusted for age, sex, education, and time between assessments	Two ways: - Global deficit score (deficit scores averaged) > 0.5 - *T* scores < 1.5 SD below published norms on 2 or more tests or 2 SD on one test	The 5% and 95% cutoffs of the summary regression-based change scores among HCs were used to classify patients with CRC as improvers, stable, or decliners (i.e., those greater than, within, or less than the 90% CI for HCs)	T1: 43% localized CRC cognitively impaired 15% HC cognitively impaired T3: 46% localized CRC cognitively impaired 13% HC cognitively impaired No significant effect of chemotherapy
Lange et al. (2016) [48]	BC	No	CT and RT groups - Pretreatment (T1) - Posttreatment (T2) Healthy group: - Same time intervals	58 CT 61 RT	*N* = 62 Healthy matched on age and education	Yes RCIpe	NR	Significant change: < 1.645: decline; > 1.645: improvement Objective measures: RCI grouped into domains. Change in a domain considered significant when at least one of the domain scores changed significantly (decline or improvement) Subjective measures: considered clinically significant when difference > 10% between T1 and T2	T1: cognitive impairment in 41% of patients (CT and RT groups) T2: cognitive decline in 49% of patients (CT and RT groups), mainly working memory No differences between CT and RT
Lyon et al. (2016) [49]	BC		- Prechemotherapy (T1) - Mid-chemotherapy (T2) - 6 months postchemotherapy (T3) - 1 year postchemotherapy (T4) - 2 years postchemotherapy (T5)	*N* = 75	No	Yes Alternate forms	Score < 70 on any dimension of cognitive test (CNS vital signs) Standard score of cognitive test: mean of 100 and a standard deviation of 15	Statistically significant differences	Improvement over time in cognitive functions but memory
Menning et al.	BC	Yes	Prechemotherapy (T1)	31	*N* = 24 (BC no CT)	Yes	Using multivariate normative	Statistically significant differences	Cognitively impaired at T2: BC: 16% No CT: 4%

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
(2016) [50]			6 months postchemotherapy (T2) Control group: similar intervals		$N = 33$ (no-cancer controls)	Multivariate normative comparison for comparing an individual's test scores against the distribution of the same scores in the control sample	comparison to classify impairment, comparing scores of each participant against the distribution of the scores of NC controls		No-cancer controls: 6%
Amidi et al. (2017) [51]	TC	Yes	- Prechemotherapy (T1) - 6 months postchemotherapy (T2)	22	$N = 42$ (active surveillance)	Yes SRB based on repeated testing of a matched healthy control group		z scores of − 1.64 or lower on the global cognitive score z or on domain level z scores	Overall cognitive decline at T2: CT group: 63.6% Surveillance group: 38.1% Marginally greater frequency of decline in verbal learning and memory: CT group: 28.6% Surveillance group: 7.5% And altered global and local brain network properties in the CT group
Andryszak et al. (2017) [52]	BC	Yes	CT group: - Prechemotherapy (T1) - Mid-chemotherapy (T2) - Postchemotherapy (T3) Healthy group: - Same time intervals	30	$N = 29$ healthy	No	NR	Statistically significant differences between groups	BC did not improve in semantic fluency. Lack of improvement indicative of learning impairment
Cerulla et al. (2017) [53]	BC	Yes	- Prechemotherapy (T1) - Postchemotherapy (T2) - 1 year postchemotherapy (T3)	25 FEC 26 FEC + T	No	Yes Sources: published articles with data on repeated testing to correct practice effects on T2 and T3	Mild impairment when scoring was found < 1SD below the normative mean on at least two neuropsychological measures Not impaired: no more than one test scored ≤ 1 SD	Statistically significant differences between groups	T2: Significant decline in both groups in measures of memory, attention, and executive functions (working memory, interference, cognitive flexibility) More tests found impaired in the taxane-added group T3: Significant decline in both groups in speed of processing, attention (sustained and divided), and in executive function (cognitive flexibility) compared to T1
Yao et al. (2017) [54]	BC	Yes	- Prechemotherapy (T1) - Postchemotherapy but presurgery (T2)	28 neoadjuvant CT	$N = 20$ healthy	Yes SRB	NR	Statistically significant differences between groups	From T1 to T3: patients did not improve as much as controls did at T3 in Stroop (evidence of cognitive dysfunction)

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
			- After surgery, 9 months postchemotherapy (T3)						Increased cognitive symptoms reported by women with breast cancer from T1 to T3
Chen et al. (2018) [55]	BC	No	- Prechemotherapy (T1) - 1 month postchemotherapy (T2)	14	*N* = 13 Age-matched women without cancer	No	NR	Statistically significant differences	No differences in neurocognitive scores between groups
Hermelink et al. (2018) [56]	BC	Yes	- Prechemotherapy (CT group) and a minimum of 1 week after negative breast imaging for control subjects (T1) - A minimum of 1 week after completion of chemotherapy or at matched intervals after T1 (T2) - 1 year after T1 (T3)	91	*N* = 58 Healthy *N* = 66 Non-chemotherapy	No	Five or more scores < 1.5 SD and/or four or more scores < 2 SD	Cognitive change = T2 and T3 cognitive scores adjusted for T1 The mean of the resulting *z*-standardized residuals across all cognitive indices = a composite score of cognitive change in relation to baseline at the respective time point	T3: decline of overall performance in patients (vs control subjects) CT group: decline in reaction time
Janelsins et al. (2018) [57]	BC	Yes	- Prechemotherapy (T1) - Postchemotherapy (T2) - 6 months postchemotherapy (T3)	580 adjuvant and neoadjuvant	*N* = 363	Yes (use of control group) but method not detailed	NR	Statistically significant differences between groups	T1 to T3: significant decline in visual memory in breast cancer patients This decline was not seen from T1 to T2 (delayed and subtle) T1 to T2: some paper-based neuropsychological tests identified significant decline. But the persistent or delayed decline was seen in the computerized, telephone-based, and single-item measures
Klemp et al. (2018) [58]	BC	No	- Prechemotherapy (T1) - After cycle 3 (T2) - Within 2–3 weeks of completing adjuvant chemotherapy (T3) - 8 years later (T4) Cognitive assessment on T1, T3, and T4	20	No	No	NR	Statistically significant differences	No change in cognitive function (significant improvement in self-regulation and planning scores)
Lange et al. (2018) [59]	BC	Yes	- Prechemotherapy (T1) - Postchemotherapy (T2)	FEC 59 FEC + T 33 Others 8	*N* = 62 Healthy matched on age and education	Yes RCIpe	If patients performed at a *z* score of ≤ 1.5 on two or more tests, or if they performed	Cognitive decline based on RCI	Five patterns of change: 36%: phase shift changes 31% impairment posttreatment (without basal impairment) 15% normal aging

Table 1 (continued)

Study	Sample	CRCI found	Time of assessment	Patients on CT	Control group?	Control for practice effect?	Cognitive impairment definition	Definition of significant decline in cognition tests	Proportion of cognitive impairment found. (impairment in chemotherapy group)
			- 6 months postchemotherapy (T3)				≤ 2.0 on a single test, they were classified as impaired		12% non-pathological decline 6% accelerated cognitive decline
Ng et al. (2018) [60]	BC	Yes	- Prechemotherapy (T1) - 6 weeks postchemotherapy initiation (T2) - 12 weeks postchemotherapy initiation (T3) - 15 months postchemotherapy initiation (T4)	108 anthracycl-ine based 58 taxane based	No	Yes RCI	NR	Patients were classified as having decline in each of the Headminder™ domains if the RCI score was lower than − 1.5	Decline in attention: T2: 20.9% T3: 15.2% Decline in memory: T2: 21.2% T3: 21.6%
Vasconcelos et al. (2018) [61]	CC	Yes	- Prechemotherapy (T1) - After 12 months (T2)	49	Yes *N* = 26 (surveillance)	No	NR	Statistically significant differences	CT group: significant decline of executive function at T2

BC breast cancer; *TC* testicular cancer; *CC* colorectal cancer; *LC* lung cancer, *Ns* not significant, *SD* standard deviation, *T* taxanes; *CT* chemotherapy; *RT* radiotherapy; *HT* hormonal therapy, *RCI* Reliable Change Index; *RCIpe* Reliable Change Index corrected for practice effects; *SRB* standard regression based, *CTC* cyclophosphamide, thiotepa, carboplatin; *FEC* 5-fluororacil, epirubicin, cyclophosphamide, *MMSE* Mini-Mental State Examination

chemotherapy, such as hormonal changes, depression and anxiety, and some genetic polymorphisms that would add vulnerability to CRCI (such as ApoE4 and COMT-Val) are among potential causes of CRCI [77].

A number of mediating variables related to disease itself and its treatment have been identified: the histopathological characteristics of the tumor, time since completion of chemotherapy, the use of hormonal therapy, dose of agents used and other secondary effects as fatigue associated to chemotherapy and radiotherapy, chemotherapy-induced menopause or sleep disturbances could have a role in the etiology of CRCI [10]. Besides, moderating variables related with health and lifestyle affect the strength or the direction of the relationship between chemotherapy and cognition. Age, cognitive reserve, cardiovascular risk factors and lifestyle habits as smoking, diet, exercise, alcohol consumption and low socioeconomic status are identified moderating factors [10].

Cognitive assessment tools

Currently, cognitive assessment with neuropsychological test is the gold standard to detect CRCI [78]. In cancer and cognition studies, it is recommended to evaluate attention, memory, speed of information processing, and executive function [79]. In this sense, the *International Cognition and Cancer Task Force* (ICCTF) [80] suggests the administration of *Trail Making Test* (parts A and B) [81], the Hopkins Learning Verbal Test (HVLT) [82], and the *Controlled Oral Word Association* (COWA) [83]. It is also recommended to add other executive function tests, based on the preferences of investigators [78]. Nevertheless, this proposal is based on the cognitive profile of women with breast cancer, while people with other type of cancer show different profiles. For example, impairment in visuospatial ability is found in patients with lung cancer [9].

There is still not a valid, reliable, and sensitive enough cognitive screening measure to detect CRCI [62]. The Mini-Mental State Examination (MMSE) [84] was designed for psychiatric patients and it is not effective to screen for subtle changes in cognition in people with cancer [85]. The Montreal Cognitive Assessment test (MOCA) [86] includes assessment of executive functions and could be more appropriate for these patients [87]. The use of specific a single-screening question has been currently investigated: "Do you think your brain is working as well as it was before your cancer diagnosis?" [88], which could be useful to detect which patients are experiencing cognitive dysfunction [89].

Methodological limitations

There are a number of methodological issues related to the study of cognitive functioning in people with cancer. The following are some of the most relevant concerns:

Lack of longitudinal studies

Since 2004, studies on cognition and cancer were cross-sectional, with different moments of assessment, a fact that hampered comparisons between results. Besides, cross-sectional studies were not useful for elucidating etiology. Incidence rates were higher in cross-sectional studies than in longitudinal studies [90].

Definition of the control group

There is no agreement about which is the most suitable group of comparison in studies on cognition and cancer. Some authors propose comparing the study group with normative data adjusted for age and education [91] or using two parallel groups (one with people with cancer without treatment and other with people without cancer). In the latter case, both groups would provide valuable information about the effects of the treatment and also the effect of cancer itself [92].

Different treatment regimens

Chemotherapy is a combination of different agents, with different mechanisms of action. Therefore, it is difficult to elucidate the neurotoxicity associated to each of these agents [93].

Different neuropsychological tests: different definitions of cognitive impairment and cognitive decline

There is great heterogeneity in cognitive tools used in studies on CRCI. It is recommended that used tests have good psychometric properties, have sensitivity, and with normative data to compare performance of the study group. It is also encouraged to introduce computerized tests to accurately assess speed of processing, although there is a lack of published data regarding validation of these tools [85].

There is no agreement about the criteria for defining cognitive impairment and cognitive decline [94]. The most frequent definition of cognitive impairment is between one and three standard deviations (SD) below normal age and education in cognitive tests [95], although in some studies there is no explicit definition. The ICCTF recommends that the definition of cognitive impairment such as 1.5 SD below the mean in two or more tests or 2 SD below the mean in one test [78]. Some authors define cognitive impairment taking into account the worsening in z or SD scores in a certain number of tests, but this option is somewhat arbitrary [94]. Besides, describing results depending on how many tests are impaired does not provide clinical information that could be useful in the design of treatment strategies [96].

Control of practice effect (PE)

PE of neuropsychological tests is an improvement in retest scores in absence of any intervention [97] because of being exposed previously to the test. This effect is found beyond the second evaluation and does not completely disappear when parallel forms of tests are used [98]. Studies with control groups use the performance of the control group to correct this practice effect with statistical methods: the Reliable Change Index corrected for practice effects (RCIpe) [99] and the standardized regression-based approach [100] are widely used, although there is no consensus about which is more accurate. In studies without control group, the PE can be corrected with published scores of adults assessed in similar time intervals [101]. Regardless of which method is used, PE must be taken into account to avoid misinterpretation of results [101–103].

Objective cognitive dysfunction versus subjective complaints

There is scientifically sound evidence that there is no correlation between complaints and objective performance on neuropsychological tests: the subjective perception of a decline in cognitive functions is correlated with depressed mood, anxiety, and quality of life [4]. Some findings suggest that objective and subjective tools to assess cognition would not measure the same construct, neuropsychological testing would not be sensitive enough to detect mild deficits or perhaps subjective complaints would reflect very subtle changes in cognition that objective tests could not detect [104].

Neuroimaging findings

Most of structural neuroimaging studies use samples of women with breast cancer treated with chemotherapy. In these patients and also in general, studies find alterations in the microstructure of white matter and impairment in cerebral networks. These impairments are evident especially when the study group is compared with a healthy control group and less evident when the comparison group is with patients with cancer but without chemotherapy. This finding would indicate cognitive impairment previous to treatment, which some authors suggest as secondary to the presence of proinflammatory cytokines released by the tumor itself that would affect the function of different neurotransmitters and cerebral network. Nevertheless, the regions that show impairments in gray matter differ between studies, without a clear pattern. There is association between structural alterations and cognitive results, although cerebral regions, cognitive domains studied, and techniques used are heterogeneous [105].

Changes in cerebral activation during specific tasks are studied in functional neuroimaging studies, with special emphasis in cognitive function found impaired in CRCI (i.e., executive function and memory). As in structural neuroimaging studies, women with breast cancer are the most studied population. Differences between patients and controls are consistently observed in frontal cortex and some areas involved in executive control and in memory processing [70, 106]. In some studies, an increasing of activation has been interpreted as a compensatory response of the brain, recruiting a wider neural network than the one that would normally been required for a particular task. In the other hand, there is also hypoactivation, interpreted as a poor recruitment of cerebral regions [107].

Some methodological issues, as different intervals of time between assessments, cancer type, methods to acquire images, and anatomic regions studied make comparisons between studies difficult. With the aim of unifying study methods, the ICCT has published a document of recommendations for neuroimaging studies [108].

Treatments

Pharmacological treatment

Different drugs have been investigated for ameliorating CRCI, but none of them has proved efficacy enough to be recommended. Methylphenidate and modafinil, donepezil, memantine, gingko biloba, and erythropoietin-stimulating agent are some of the drugs used with conflicting results. Larger studies are needed to establish the clinical value in an oncology setting [109].

Non-pharmacological treatment

Some non-pharmacological approaches are found to be effective for improving cognition and quality of life with people with cancer-related cognitive problems; most of these published studies assessed women with breast cancer [110, 111]. Some aspects are common across different interventions: (1) information about CRCI with the aim to validate complaints and adjust expectations about the trajectory of the cognitive impairment; (2) identifying situations that place the person at risk for memory mistakes; and (3) management of distress (training in relaxation techniques, improvement of sleep quality…) and training for using compensatory strategies, both external memory aids (lists, calendars, alarms) and internal strategies (as self-instructional training). The Memory and Attention Adaptation program (MAAT) [112] has shown improvement in speed of information processing and in self-reported cognitive function compared with an active control group [113].

Cancer, chemotherapy, and aging

Subjective complaints in cancer patients with CRCI are very similar to those found in older adults. Gray matter

volume reductions, loss of integrity of the white matter fiber, and changes in cerebral activity during some tasks have been found both in people treated with cancer and in normal aging [72]. Nevertheless, there are few studies exploring cognitive trajectories of older adults with cancer [114]. Mechanisms involved in CRCI in older adults are more complex because they can have comorbid medical conditions that can increase vulnerability to CRCI through similar mechanisms, they can be treated with drugs that can interfere with cognitive function, and they may need more changes in dose or type of treatment that also can have an impact on cognition [115].

Regarding the impact cancer treatment has on cognitive function, there are currently two non-mutually exclusive hypotheses: the phase shift hypothesis proposes that patients treated for cancer experience cognitive declines slightly worse than those without cancer or treatment for cancer, but parallel to healthy population over time. The accelerated aging hypothesis asserts that patients with cancer may experience steeper declines in cognitive function compared to non-cancer populations [114]. The scarce studies on the cognitive trajectory of old patients with breast cancer find different patterns of change between the pre- and posttreatment assessments, being the accelerated aging the most frequent trajectory that is found [87, 116]. Risk factors for one or other trajectory of cognition through time are not known [117].

Conclusion

In conclusion, chemobrain is frequent in patients treated for cancer that can start anytime through the disease process and is related with chemotherapy. In some patients, cognitive impairment is also found before treatment. Subjective concerns are similar across patients, but the neuropsychological pattern is slightly different regarding type of cancer and type of treatment. Attention, memory, and executive functions are frequently impaired, although visuospatial and visuoconstructional abilities can also found impaired. Chemobrain is mild but with great impact on quality of life and it is not related to depression or anxiety. Therapeutic options are still limited, with evidence regarding non-pharmacological approaches as cognitive training that includes the learning of compensatory strategies to minimize or prevent memory failures. There is still lack of information about causal mechanisms, risk factors, and relationship between cancer, aging, and neurodegeneration.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This review does not contain any studies with human participants performed by any of the authors.

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