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Cancer-related cognitive impairment in survivors of adolescent and young adult cancer: A scoping review

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Conflict of Interest Statement

No conflict of interest has been declared by the authors.

Abstract

Objectives: Cancer-related cognitive impairments (CRCI) are common after treatment and could have important repercussions for adolescent and young adult (AYA) survivors diagnosed between ages 15 and 39. However, most research focuses on younger or older survivors so we know relatively little about CRCI among AYA cancer survivors. Here we review the research on CRCI among survivors of AYA cancer to determine prevalence, associated factors, and ongoing impact.

Methods: In December 2020 we performed a systematic search in MEDLINE, Web of Science, PsycInfo, CINAHL, EMBASE, and Cochrane Central Register of Controlled Trials to identify peer-reviewed English language articles describing original research with survivors of AYA cancer having at least one outcome concerning cognition. We

screened 4090 articles and 35 met eligibility criteria. Guided by the PRISMA-ScR Checklist, we extracted information, assessed study quality, organized articles by study design, identified factors associated with CRCI, and identified ongoing impacts of CRCI.

Results: Most studies were cross-sectional surveys and interviews with some longitudinal and neurocognitive assessment studies, one brain imaging study, and one intervention study. Weighted mean prevalence of CRCI was 38.4%. Factors associated with CRCI included older age, female gender, higher dose chemotherapy, and comorbidities. Ongoing impacts of CRCI included impaired role functioning, financial toxicity, and unmet needs. However, the intervention study had encouraging results for improving cognition and functioning.

Conclusions: This review of literature on CRCI in survivors of AYA cancer shows a need for longitudinal, imaging, and intervention studies. Digital health technology is recommended for research and intervention implementation.

Keywords: Cancer, oncology, cancer survivors, adolescent, young adult, cognitive dysfunction, chemotherapy-related cognitive impairment, review

Background

In the United States, about 89,500 adolescents and young adults (AYAs)—those between ages 15 and 39¹—were diagnosed with cancer in 2020². The impact of cancer on cognition is a concern for many of these survivors as the disease and its treatments disrupt a critical period of rapidly developing behavioral and emotional skills and social role³. Although cancer survivors regularly report cognitive issues after treatment, these needs are often unaddressed⁴. The literature on cognitive function specifically in AYA cancer survivors is sparse, making it difficult to provide evidence-based assistance. This review aims to characterize the evidence for cancer-related cognitive impairments (CRCI) in AYAs so that providers can deliver appropriate support during survivorship.

Cognition and cancer

A growing evidence base supports the lasting impact of cancer and its treatment on cognitive function^{5–8}. Cognitive functions typically affected are memory, attention, executive function, and processing speed⁹, resulting in negative impacts on quality of life¹⁰. Reported prevalence of CRCI ranges widely from 6 to 68% in children⁶ and from 17 to

75% in adults¹¹. Some factors thought to influence measures of prevalence are the cancer diagnosis and treatment, cognitive assessment methods, and CRCI definitions.

Cancer diagnosis and treatment

Some CRCI is attributable to cancer itself. Central nervous system (CNS) cancers are most likely to result in CRCI due to a direct effect on brain tissue⁸, but non-CNS cancers are also thought to contribute to CRCI; most of the research is with female breast cancer survivors^{8,9}. Some research suggests that non-CNS cancers affect cognition even prior to diagnosis⁸, while other studies suggest that differences in cognition for cancer patients may be due to post-traumatic stress from receiving the cancer diagnosis or selection bias in research studies^{12,13}. Although colloquial references such as “chemo-brain” or “chemo-fog” suggest that chemotherapy is primarily responsible for CRCI^{8,9}, evidence indicates associations between CRCI and other therapies such as radiation or surgical resection as well⁸.

Cognitive assessment

Cognitive function can be assessed using either objective neuropsychological batteries, which measure performance in specific domains, or subjective patient self-reports, which give insights into the patient’s experience of their cognitive capacity. The outcomes differ, with objective impairment being less prevalent than subjective impairment in cancer survivors¹⁴. Evidence suggests that subjective cognitive deficits are strongly correlated to depression, anxiety, or fatigue and only weakly correlated to objectively measured cognitive impairment¹⁵.

There is also very little concordance in the assessments researchers use, hindering comparison between studies. In 2011, the International Cognition and Cancer Task Force (ICCTF) issued a recommended objective assessment battery that takes about 35 minutes to complete with supplemental tests that add 10 to 90 minutes each¹⁶. In 2021, the Cancer Neuroscience Initiative Patient-Reported Outcomes Working Group issued a recommendation for the subjective Patient-Reported Outcomes Management Information System (PROMIS) Cognitive Function Short Form 8a¹⁷.

Definition of cognitive impairment

In addition to the measures, the criteria for cognitive impairment vary from study to study. The ICCTF recommends that CRCI be defined as scoring 1.5 standard deviations below the mean on two or more neurocognitive assessments or 2 standard deviations below the mean on one neurocognitive assessment¹⁶, but this definition isn't universally adopted. The lack of standardization inevitably impacts the prevalence reported in the literature. Schilder et al.¹⁸ found that prevalence ranged from 1% to over 45% depending on CRCI criteria and reference group.

Considerations for adolescents and young adults

Although AYAs are diagnosed with cancer at about eight times the rate of children age 14 and under, much of the evidence providers reference to manage late effects in AYAs comes from the literature on survivors of childhood cancer^{19,20}. However, studies show that AYAs are not just "big children" and providers need a reliable evidence base to deliver appropriate care to this age group²⁰.

The adolescent and young adult years are a critical period of physical, cognitive, social, and emotional development, and a cancer diagnosis during this period can have a lasting impact on the patient's entire life course³. Evidence on brain development indicates that the frontal lobe and amygdala mature and develop into the 20s and the hippocampus begins to decline after age 30²¹, and each is more vulnerable to stress during those times. Particularly during adolescence, exposure to highly stressful or traumatic events such as life-threatening illness is a predisposing factor for developing conditions such as major depressive disorder and anxiety-related disorders²². Cancer and its treatment can also disrupt the important developmental milestones of adolescence and early adulthood, including those related to cognition, and change educational and career trajectories⁹. Further compounding these impacts, adolescents and young adults often do not have the social or material support that is more available to patients who are older or younger²³. All of these factors can affect cognitive health and have lasting impacts beyond adolescence or young adulthood.

Objectives

In an effort to organize the evidence concerning CRCI in survivors of AYA cancer, this review collates the original research on cognitive symptoms, identifies gaps, and specifies priorities for future research. We aim to answer the following research questions:

- (1) What is the evidence for prevalence of CRCI among survivors of AYA cancer?
- (2) What is the evidence for the factors associated with CRCI among survivors of AYA cancer?
- (3) What is the evidence for the ongoing impacts of CRCI on survivors of AYA cancer?

Method

Overview

Using the PRISMA-ScR scoping review methods²⁴, we conducted a scoping review to organize the original research on CRCI in survivors of AYA cancers.

Inclusion Criteria

Inclusion criteria were: (1) full-text article in a peer-reviewed venue, (2) English language, (3) original research with survivors of cancer diagnosed between the ages of 15 and 39 or stratified by age, and (4) at least one measurement concerning cognition. To incorporate the range of research on AYA survivors, we included research with both qualitative and quantitative measurements. For studies including participants outside of the 15 to 39 age range, we included articles if results were reported by age group or if over half of the participants were age 15 to 39 at diagnosis. Considering the paucity of research on AYAs, we made this decision in an attempt to be as inclusive as feasible. We excluded studies examining only central-nervous system cancers since CRCI are expected and more severe for these survivors.

Data Sources and Search Strategies

We completed a systematic search in December 2020 for relevant articles indexed in Pubmed, Web of Science, PsycINFO, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Excerpta Medica dataBASE (EMBASE), and the Cochrane Central Register of Controlled Trials (CENTRAL). Search terms included phrases indicating adolescent and young adult age, cancer survivor, and cognitive impacts. We also searched several phrases that are associated with cognition in cancer survivors such as “impairment”, “late effects”, and “unmet needs.” An example search string for PubMed is:

("adolescent"[All Fields] OR "young adult"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND (("cognition"[MeSH Terms] OR "cognition"[All Fields]) OR "late effects"[All Fields] OR "unmet needs"[All Fields])

We also reviewed references of screened articles for additional literature.

Procedure

Our search yielded 4090 articles. Using Covidence software to manage the review process, we removed 1349 duplicates then screened 2741 abstracts. Two people independently screened each abstract and conflicts were reconciled through consensus with one author (LMV) being the final arbiter. We then screened 290 full-text articles in the same manner resulting in 35 articles for synthesis. The PRISMA flow diagram for the screening process is in Figure 1.

Figure 1: PRISMA flow diagram

Extraction and Charting of Results

We extracted information related to the objectives of the review: study methods, participant details, study measures, CRCI findings, and any results concerning prevalence, associated factors, or ongoing impacts of CRCI. Extracted information was independently verified by a research assistant and articles were organized according to methods and findings. Prevalence of CRCI was calculated through weighted means and medians across the studies. Based on the extracted results, two researchers independently formed themes around the factors associated with

and impact of CRCI, and theme descriptions were harmonized through discussion. We appraised study quality using the Mixed Methods Appraisal Tool²⁵ due to the inclusion of both quantitative and qualitative data.

Results

Evidence from the 35 included articles is organized in Appendix 1 by research method (quantitative, mixed, or qualitative) and includes study and participant details, measures of cognition, significant cognitive outcomes, and quality appraisal. Twenty-two studies used quantitative methods, four employed mixed methods, and nine utilized qualitative methods.

First, we characterize the extent of research and methods used. Next, we report the weighted average prevalence, associated factors, and ongoing impacts of CRCI among AYA cancer survivors.

Extent of research

Publications per year

Figure 2 shows the yearly trend of publications on AYA CRCI. We see higher interest in 2012 and 2013 followed by a 3-year lull and a recent upswing starting in 2017.

Figure 2: Articles published per year on CRCI in AYA cancer survivors

Types of research

Data collection

Articles described a wide range of data collection methods including surveys, interviews, cognitive assessments, focus groups, brain imaging, and intervention. Five articles reported results of longitudinal studies and the other 30 reported results of cross-sectional studies. Figure 3 shows data collection methods by cross-sectional and longitudinal designs. Some studies used more than one method.

Figure 3: Data collection methods used

Cognitive measures

For the 26 quantitative and mixed method studies, validated self-report instruments were used in 66% of studies, standard neuropsychological assessments in about 9%, and investigator-developed instruments in 25% (Figure 4). Of the longitudinal studies, four used self-reported outcomes^{36,40,45,50} and one utilized neurocognitive assessments⁴⁸. Qualitative studies did not specifically assess cognition, instead allowing cognitive concerns to emerge organically, so those are not included in the figure.

Figure 4: Cognitive measures used in quantitative and mixed methods studies

Two studies used both objective and subjective cognitive measures^{39,47}. Nugent et al.³⁹ found no significant difference between survivors and controls on objective measures but did find small and medium effect sizes and a significantly higher rate of subjective memory problems among survivors. Trachtenburg et al.⁴⁷ reported that survivors scored significantly lower than controls on multiple cognitive measures and that objective and subjective measures were correlated.

Prevalence of CRCI in AYAs

We included 10 articles in the calculation of mean prevalence weighted by number of participants (Table 1). One article reported prevalence based on validated objective neurocognitive assessments while the rest relied on self-reports. For articles reporting more than one prevalence we used the most conservative number. We calculated a median prevalence of 49% and a weighted mean of 38.4%. This is consistent with other estimates of around 35% for ongoing cognitive problems after cancer treatment^{5,8}. We excluded two studies from our calculations because we could not determine an estimate of prevalence of cognitive problems for AYAs (noted in Table 1).

Table 1: Prevalence of CRCI reported per article

Article	N	Prevalence	
Objective assessment			<u>Weighted Mean</u> 38.4%
Wefel et al. ⁴⁸	11 no chemotherapy	0% no chemotherapy	
	23 low chemotherapy	52% low chemotherapy	
	28 high chemotherapy	67% high chemotherapy	

Self-report – included in prevalence calculation			<u>Median</u>
Prasad et al. ⁴¹	1054 survivors	13.9% impaired task efficiency 21.6% impaired memory	49%
Ketterl et al. ³⁵	872 survivors	54.2% task interference	
Szalda et al. ⁴⁶	611 survivors	56% neurocognitive concerns	
Jones et al. ³³	575 survivors	49% cognitive changes	
Rey et al. ⁴²	222 survivors	>=36.5% at each timepoint	
Stevens et al. ⁶¹	55 survivors	46% “brain fog”	
McLoone et al. ⁵⁹	19 survivors	50% student-reported	
Armin et al. ⁴⁹	19 survivors	47% cognitive impact	
Fauske et al. ⁵⁶	18 survivors	83% some cognitive impact	
Self-report – not included in prevalence calculation			Exclusion reason
Huang et al. ³⁰	604 survivors	32% cognitive concerns	Reported influence of age but did not stratify results
Vetsch et al. ⁵²	42 survivors	69% interviewer-rated impairment	Rating included physical and cognitive impairments

Factors associated with CRCI in AYAs

Structural differences in the brain and individual factors such as treatment type, cancer type, age, gender, and comorbidities are associated with CRCI in AYAs.

Structural differences in the brain

In the single imaging study, Apple et al.²⁶ found that, compared to controls, survivors show more inward hippocampal deformation, worse cognitive functioning, and lower episodic memory test scores, which is consistent with evidence that the hippocampus begins to decline after age 30 and is more vulnerable to stress or disease during that time²¹.

Cancer Treatment Type

Five studies investigated an association between cognitive issues and cancer treatment type. Two examined the role of chemotherapy with survivors of testicular cancer^{43,48}, two examined the impact of chemotherapy with or without radiotherapy on survivors of Hodgkin lymphoma^{36,47}, and one examined the effects of chemotherapy, radiation, and surgery stratified by age and cancer type³⁵. Skoogh et al.⁴³, Wefel et al.⁴⁸, Trachtenberg et al.⁴⁷, and Ketterl et al.³⁵ reported associations between chemotherapy and cognitive issues for all cancer types, although some cancers showed lower risk than others. Ketterl et al.³⁵ also found a link between cognitive issues and radiation treatment for breast cancer, as well as a link between surgery and cognitive issues for less common cancers, including sarcoma, germ cell tumors, skin cancer and brain tumors. In contrast, Kreissl et al.³⁶ found no effect of treatment type, including chemotherapy, on cognitive outcomes for Hodgkin lymphoma.

Studies also found 'dose-response' relationships with higher levels of chemotherapy being associated with increased reports of cognitive difficulties. Skoogh et al.⁴³ and Trachtenberg et al.⁴⁷ found dose-response relationships with the number of chemotherapy cycles, while Wefel et al.⁴⁸ noted the relationship with chemotherapy dosing. However, researchers could not determine whether decline was due to the dose or the specific chemotherapy regimen.

Ketterl et al.³⁵ found that breast cancer survivors who had radiation or chemotherapy had higher mental impairment at work, which was also found with survivors of cancers other than breast cancer, leukemia, lymphoma or thyroid cancer who underwent chemotherapy or surgery.

Cancer Type

A handful of studies examined the impact of cancer type on cognition. Husson et al.³² found that worse cognitive outcomes were associated with having had leukemia, Hodgkin's lymphoma, or a cancer with a lower survival rate, while Prasad et al.⁴¹ found that survivors of lymphoma and sarcoma were at lower risk of neurocognitive problems than survivors of leukemia. Nowe et al.³⁸ found that breast and gynecological cancer survivors reported higher cognitive fatigue while testicular cancer survivors reported lower cognitive fatigue. Smith et al.⁴⁴ found no association between cancer type and work or school functioning.

Age

Most studies that examined age and cognitive impairments found that older age was associated with higher levels of impairment^{31,36,45,46,56}. However, one article reported that younger survivors had more cognitive impairment⁴⁸, one found that younger survivors reported worse functioning⁴⁴, and one found no difference in cognitive function between older and younger survivors²⁸.

Gender

In the studies that compared outcomes by gender, all reported worse cognitive outcomes for female survivors^{31,32,36,38}. Kreissl et al.³⁶ found that women reported higher cognitive deficit at all timepoints in their study. Husson et al. report that female AYA lymphoma survivors scored significantly worse on cognitive functioning compared to male survivors³¹, and female AYA survivors of any cancer scored significantly higher on the negative IOC summary scale and cognitive function subscale compared to male survivors³². Higher cognitive fatigue was also associated with being female in the study from Nowe et al.³⁸.

Comorbidities

Worse cognitive outcomes were often associated with comorbid conditions, most often fatigue and mental illness. Husson et al.^{31,32} found that worse cognitive function was associated with having physical fatigue or having two or more comorbid health conditions such as diabetes or asthma. Similarly, Nowe et al.³⁸ report an association between cognitive fatigue and having other health conditions.

Several articles reported that high physical fatigue and low cognitive function are comorbid and some suggest that they may be tightly coupled^{31,32,39,45}. Husson et al.^{31,32}, Kreissl et al.³⁶, and Nugent et al.³⁹ report correlations between worse perceived cognitive function and physical fatigue. Furthermore, Stadtbauer et al.⁴⁵ showed that improvements in cognition reduced physical fatigue more than reductions in physical fatigue improved cognition. In contrast, Trachtenberg et al.⁴⁷ found that although both physical fatigue and cognitive issues were common, they were not associated with each other in their sample of Hodgkin lymphoma survivors.

Mental illness is common in cancer survivors⁶² and several articles in this review reiterated that conclusion³³, but some went further to investigate the association between mental and cognitive health. Husson et al.^{31,32}, Nugent et al.³⁹, and Rey et al.⁴² all found correlations between cognitive problems and symptoms of depression and/or anxiety. Furthermore, Kreissl et al.³⁶ found that worse cognitive function was strongly correlated with worse emotional function both 2 and 5 years after treatment.

Ongoing impacts of CRCI in AYAs

After treatment, cognitive issues have an ongoing impact on survivors' lives. We first describe the contextual evidence contributed by qualitative and mixed methods studies. Next, we examine the reported ongoing consequences associated with reduced cognitive function, and discuss the results of one intervention study designed to assess ability to mitigate ongoing difficulties in survivorship.

Lived experience and characterization of cognitive function

The survivor voice comes through in the mixed method and qualitative studies, giving powerful context for the results from the quantitative measures. Possibly due to a perceived lack of preparation for cognitive issues in survivorship⁵¹, survivors feel "overwhelmed" and "surprised" by the impact of changes in cognition^{53,63}. They indicate a sense of loss⁵⁸, experience difficulty adjusting to changes⁶⁰, report "forgetting" or difficulty "keeping up"⁴⁰, and find that cognitive issues are often more difficult for them to handle than some other symptoms because they are "invisible"⁵⁵. Participant described frustration with their concentration problems, with one saying that "I [lose] my train of thought like immediately."⁵² Survivors also expressed a mismatch between their initial expectations of what their cognitive abilities would be and the poorer reality that they experienced later⁵⁰.

Role Functioning

By far the most common theme across articles was that cognitive complaints are associated with difficulties in role functioning^{27,35,39,41,44,50,52–59}. Survivors commonly reported worse concentration, memory, and attention^{33,34,40,44,47,52,53,58} and were concerned about the negative impacts of these deficits on employment and education^{27,39,40,47,53,58,59}. Husson et al.^{31,32} showed that worse cognitive function was associated with being

unemployed. Unemployment was associated with self-reports of impaired task efficiency⁴¹ and with lower education levels⁴² in the AYA population.

However, a substantial proportion of survivors who report worse cognition after treatment are able to return to work or school. Parsons et al.⁴⁰ report that over 72% of those either working or in school full-time prior to diagnosis returned to work or school even though 30% still endorsed problems with “paying attention” and 28% reported troubles “keeping up with work or studies.” However, only 34% of those who worked or were in school part-time had returned to that level. Cheng et al.²⁷ found that, compared to controls with similar backgrounds and jobs, cognitive symptoms at work were related to lower quantity, quality, and timeliness of completed work. Ketterl et al.³⁵ found that breast cancer survivors treated with chemotherapy or radiation had more cognitive problems at work.

Ongoing financial problems may also be related to an association between cognitive problems and unemployment or difficulties in the workplace or school. Nowe et al.³⁸ found that worse cognitive fatigue is associated with worse financial problems and Kreissl et al.³⁶ determined a moderate correlation between worse cognitive function and worse financial health at both 2 and 5 years after treatment.

Quality of life

Several studies reported lower quality of life related to cognitive problems for AYA survivors^{30,31,36,42,50,56}. Husson et al.³¹ surveyed lymphoma survivors and age- and gender-matched controls and found that survivors reported significantly worse scores in the cognitive domain of a health-related quality of life measure. In interviews with survivors, Fauske et al.⁵⁶ found that participants with pronounced cognitive difficulties expressed that their lives had completely changed and that they were struggling to cope. Huang et al.³⁰ found that higher levels of cognitive disturbance was associated with significantly lower quality of life.

In a longitudinal analysis, Kreissl et al.³⁶ report that worse cognitive function is correlated with worse health-related quality of life in most domains from baseline through 5 years after treatment. Related to these findings, Rey et al.⁴² advise that since reports of cognitive impairment are common and affect quality of life, long-term complaints of cognitive impairment deserve greater consideration than they are currently afforded.

Unmet information and support needs

Survivors often expressed that needs around cognitive issues were unmet^{33,34,51,54,60,61}. Jones et al.³³ found that only 41% of survivors with cognitive concerns sought help and 47% of those experienced difficulty finding help. Similarly, Stevens et al.⁶¹ found that although 46% of participants wished for support in dealing with “brain fog,” fewer than 5% were actually offered support. AYA survivors were also disappointed in the lack of resources and support they received⁵⁵ and they specifically want better access to cognitive assessment and rehabilitation resources⁵⁴.

Rehabilitation

Although survivors can experience difficulty obtaining help with cognitive problems, we were encouraged by the positive results of the intervention study from Hauken et al.⁵⁰. The authors tested a rehabilitation program for AYA cancer survivors with 20 participants and demonstrated a significant improvement in cognitive function from baseline through the end of the program. Importantly, those improvements were sustained during the follow-up period. Although cognitive function did not reach the level of the normative group, the study shows that declines can be somewhat mitigated or reversed. Furthermore, participants expressed high satisfaction with the program, high achievement of program goals, and high adherence to the program. They also recognized that they had learned new skills, gained new control, and could apply the skills and control in an ongoing rehabilitation process.

Discussion

The literature indicates that cancer-related cognitive symptoms are real and are challenging for survivors to manage. Although some survivors are able to obtain help with cognitive issues, most say that their needs are not adequately met. That lack of support can potentially complicate resumption of education and career and contribute to financial toxicity.

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3 **Limitations of current CRCI research with AYAs**
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6 This review surfaces several issues around how research in cognition and survivorship is conducted and reported.

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8 These include:

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10 1. Lack of consistent cognitive measures
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12 2. Lack of consistent terminology
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14 3. Lack of specification of comorbidities
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16 4. Lack of stratification by participant age
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18 5. Lack of longitudinal studies
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22 **Cognitive Measures**
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24 Perhaps the biggest issue inhibiting progress in this area is the lack of consistency in cognitive measures. The
25 studies in this review used 12 different published scales, three different cognitive batteries, and several
26 investigator-generated scales. This emphasizes the absence of a gold standard for assessing cognition in the cancer
27 survivor population and makes comparisons and meta-analyses difficult. The assessment battery recommended by
28 the ICCTF is appropriate for clinical use, but may be too time-intensive for research purposes. The most common
29 instrument used in in this review, the subjective EORTC QLQ-C30, averages about 11 minutes for administration as
30 compared to the base 35 minutes required by the ICCTF battery. However, objective and subjective assessments
31 appear to measure different constructs with objective assessments measuring performance and subjective
32 assessments giving insight into the patient’s experience. Although objectively measured impairment is less
33 prevalent than subjectively measured impairment¹⁴, the possible correlation between objective and subjective
34 cognitive assessments reported by Trachtenberg et al.⁴⁷ implies that clinicians may at least be able to use self-
35 report measures for screening rather than referring the bulk of survivors for expensive and time-consuming
36 objective cognitive assessments.
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51 Results from individual studies are likely to be highly dependent on the assessment used, the diagnoses and
52 treatments included in the sample, as well as the sampling method, further complicating direct comparisons
53 between studies. However, it is clear that a sizable portion of AYAs consider themselves to have impaired cognition
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3 compared to their capabilities prior to cancer and in all studies comparing prevalence between survivors and a
4 control group, AYA survivors reported higher levels of cognitive issues^{30,33,41}. Survivors often perceive cognitive
5 problems although objective cognitive assessments show function within norms. This phenomenon may occur for
6 several reasons (see ¹⁵ for a comprehensive treatment), including that the decline may be too subtle for objective
7 assessments to detect or that prior functioning was above norms. Furthermore, unlike people experiencing
8 cognitive declines due to dementia or aging, AYA survivors are usually able to offer insight concerning their own
9 functioning and reliably report their experiences. Many objective measures currently available were not developed
10 to detect subtle decline⁶⁴ and that problems not detected by objective measures are no less real or worrisome to
11 those experiencing them¹⁷.
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23 Terminology

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25 The words articles use to refer to cancer-related cognitive impairment are inconsistent. Some articles discuss
26 specific cognitive domains, including attention, concentration, thinking, or memory, while others use more
27 colloquial terms, such as “chemo-fog”⁵⁸, “brain fog”⁶¹, and “chemo brain”⁶⁰. A lack of precise and common
28 terminology in reporting makes it difficult to readily identify all articles that investigate cancer-related cognitive
29 impairments. Qualitative studies illustrate that many survivors think of chemotherapy as primarily contributing to
30 cognitive issues when they use phrases like “chemo brain”⁶⁰ and “chemo-fog”⁵⁸. However, chemotherapy seems
31 to be only one of several factors involved in developing CRCI, and such language may reveal a problematic bias by
32 attributing cognitive issues only to chemotherapy.
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43 Comorbidities

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45 Many articles examine comorbidities as a factor affecting function in survivors and one of the comorbidities
46 included is often impaired cognitive function. However, articles commonly report the number of comorbidities
47 without specifying frequencies of individual comorbidities. A variation is articles that examine “unmet needs” or
48 “late effects”, one of which is often impaired cognitive function, but also do not specify frequency of particular
49 needs or late effects. As with a lack of common cognitive measures, this lack of specificity makes comparisons and
50 meta-analyses difficult and impedes investigation of relationships among comorbidities, needs, and late effects.
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Participant ages

Studies often include AYAs in their samples but do not stratify by age or analyze age groups separately. However, stratification or grouping by NCI-defined age groups is important to identifying differences attributable in part to developmental differences between those age groups. It would also be helpful for articles to note age at diagnosis, age at study, and time since end of active treatment.

Longitudinal studies

Only five of the 35 articles in this review reported results of longitudinal studies. Although cross-sectional studies offer important insights, a relative lack of longitudinal studies hampers our ability to characterize the nature and trajectory of cognitive issues for AYA cancer survivors over time.

Clinical Implications

Based on the review of research on CRCI in survivors of AYA cancer, we have several recommendations for future research.

Well-characterized participant samples and control groups

In addition to specifying treatment regimen, cancer type, gender, age at diagnosis, time since end of active treatment, and comorbidities, studies of cognitive function should characterize risk factors associated with lower cognitive function such as PTSD, fatigue, and childhood trauma and stress^{7,21,65,66}. This is particularly important as PTSD and fatigue are highly prevalent in AYA cancer survivors. Studies with well-characterized samples will help us better identify relationships among those characteristics in terms of impact on cognition.

Standard cognitive measures

Researchers need a battery of objective and subjective measures built around a brief core general assessment supplemented with recommendations for tests in specific domains as needed. This approach would institute a usable standard that enables researchers to assemble batteries that meet study objectives as well as time and

resource constraints. To further support meta-analyses and comparison between studies, articles should also report subscale scores in addition to composite scores (ex. cognitive domain of EORTC QLQ–C30).

Longitudinal research

The lack of longitudinal studies is a crucial barrier to accurately characterizing the course of cognitive problems in survivors of AYA cancer.

Intervention research

The one article on rehabilitation gave encouraging results for improving function in survivors of AYA cancer⁵⁰. Trials of non-pharmacological and pharmacological interventions with other age groups also show promising results^{5,7,8}. Survivors of AYA cancer have long life expectancies during which to contribute to society so interventions targeted to this population are critical to helping them overcome cognitive impairments.

Cognitive neuroscience research

Apple et al.'s²⁶ imaging study showed structural differences between the brains of AYA breast cancer survivors and controls, pointing to a need for further imaging and other cognitive neuroscience research. Studies using EEG, MRI, fMRI, fNIRS, and other methods are needed to identify changes in the brains of cancer survivors before, during, and after undergoing different therapies and their relationship to function.

Technology use

The inconvenience and logistical challenges associated with research participation are particularly burdensome for underserved groups who are often underrepresented in research—those who are young, single, low-income, or unemployed⁶⁷. Effective use of technology can help lower these barriers, enabling people to participate who might otherwise be unable. Mobile health technologies are especially attractive for reaching younger people since 96% of those ages 18 to 29 in the US own a smartphone, and many younger, lower-income, and non-white Americans depend on a smartphone as their only means of internet access⁶⁸. Beyond the research phase, technology is also a scalable means of implementing assessments and delivery of interventions^{8,69}.

Study Limitations

Due to the aforementioned variability in definitions and measurements for CRCI, as well as the diversity of cancer types and treatments across studies, estimates of CRCI prevalence in different AYA survivor populations need to be confirmed with further research. Inconsistency in terminology around cognitive impairment also may have limited our ability to comprehensively identify all publications measuring CRCI in AYA populations. Despite these limitations, this review provides broad guidance for future research exploring the impact and treatment of CRCI in AYA cancer survivors.

Conclusion

Lingering cancer-related cognitive impairments are common after treatment ends and can have long-term consequences for survivors, especially adolescent and young adult survivors pursuing an education or career. To advance the goal of developing age-specific guidelines for mitigating CRCI for AYAs this review collated the original research on cognitive symptoms, identified gaps, and specified priorities for future research. Factors positively associated with CRCI were older age, female gender, higher dose chemotherapy, and comorbidities. Ongoing impacts of CRCI are impaired role functioning and unmet needs. However, the encouraging results from the single intervention study proved the viability of a program to improve cognition and functioning in AYA cancer survivors. Additional longitudinal and intervention studies, particularly those leveraging digital health technologies, are necessary to develop evidence-based CRCI mitigation strategies for survivors of adolescent and young adult cancer.

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For Peer Review

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Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
Quantitative					
Apple (2017)²⁶	Cross-sectional imaging study	Age 18-45: <ul style="list-style-type: none"> • 16 pre-menopausal breast cancer survivors • 18 controls 	Hippocampal deformation, Neuro-QOL Cognitive Function, NIH Toolbox Cognition Battery	<ul style="list-style-type: none"> • Compared to controls, survivors show more inward hippocampal deformation, worse cognitive functioning, and lower episodic memory test scores. • Compared to controls, survivors reported significantly more general cognitive concerns. 	Limited sample, risk of biased sample (40%)
Cheng (2018)²⁷	Cross-sectional survey	Ages 20-60 at survey, >2 years post-treatment: <ul style="list-style-type: none"> • 267 breast cancer survivors • 267 controls 	BRFSS job stress, HADS, EORTC QLQ-C30, CSC-21, WLQ output scale	<ul style="list-style-type: none"> • After correcting for age, depression, anxiety, and fatigue, having more cognitive symptoms is related to lower quantity, quality, and timeliness of work for survivors but not controls. 	Risk of biased sample and non-response bias (60%)
Hall (2012)²⁸	Cross-sectional survey (Cancer Survival Study)	<ul style="list-style-type: none"> • 58 survivors age 18-40 at diagnosis • 58 gender and cancer-type matched older adults 	SCNS-SF34, EORTC QLQ-C30, items on smoking, alcohol consumption, and physical activity	<ul style="list-style-type: none"> • No significant difference between younger and older survivors on cognitive functioning. • No comparison to normative data is given in the article but the mean score is not significantly lower than published normative data adjusted for age ²⁹. 	None (100%)
Huang (2017)³⁰	Cross-sectional interview	604 survivors, 6166 controls:	NHIS symptom and cognitive disturbance	<ul style="list-style-type: none"> • Overall, survivors experienced more cognitive issues than controls (32% vs. 21%), but younger survivors 	None (100%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
	(National Health Interview Study)	<ul style="list-style-type: none">• Age 18-44: 53 survivors, 3082 controls• Age 45-64: 229 survivors, 2028 controls• Age >64: 322 survivors, 1056 controls	questions, Global Health Scale (PROMIS)	<ul style="list-style-type: none">• had significantly less CRCI. Prevalence was not reported by age.• Cognitive disturbance was associated with significantly lower mental and physical quality of life for all ages.	
Husson (2017) ³¹	Cross-sectional survey	<ul style="list-style-type: none">• 198 lymphoma survivors age 18-39 at diagnosis• 380 age-and sex-matched controls	EORTC QLQ-C30, HADS	<ul style="list-style-type: none">• Compared to controls, survivors scored significantly worse on cognitive HRQoL domains• Low HRQoL associated with being female, unemployed, having comorbid conditions, fatigue, anxiety, depression	None (100%)
Husson (2017) ³²	Cross-sectional survey	173 survivors age 15-29 at diagnosis and 18-39 at study	IOC-AYA version, SF-36, BSI-18	<ul style="list-style-type: none">• Lower cognitive function associated with being female, being unemployed, and having had leukemia, current health problems, distress, or a cancer with lower survival rate	Risk of biased sample and non-response bias (60%)
Jones (2020) ³³	Cross-sectional survey (Transitions Study)	575 survivors ages 18-34 within 5 years of completing treatment	Surveys to identify unmet needs and associated risk factors	<ul style="list-style-type: none">• 49% reported changes to concentration and/or memory.• 41% sought help for cognitive changes and 47% of those had difficulty obtaining help.	Risk of biased sample and non-response bias (60%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
Keegan (2012) ³⁴	Cross-sectional survey (AYA-HOPE survey)	523 survivors age 15-39 at diagnosis	Self-reported needs and outcomes, chart abstraction	<ul style="list-style-type: none"> Survivors are more likely than patients to have an unmet need. Having more than three symptoms (including problems with memory, concentration, or attention) was associated with having unmet needs. 	Risk of biased sample and non-response bias (60%)
Ketterl (2019) ³⁵	Cross-sectional survey	872 survivors age 18-39 at diagnosis, >1yr since treatment and 1-5yr since diagnosis	Online survey related to physical and mental impairment, work, and finances; medical chart abstraction	<ul style="list-style-type: none"> 54.2% reported interference with mental tasks at work or in studies Higher mental impairment at work for breast cancer survivors was associated with radiation or chemotherapy. Higher mental impairment at work in 'other' cancer survivors was associated with chemotherapy or surgery. 	Risk of biased sample and non-response bias (60%)
Kreissl (2020) ³⁶	Longitudinal survey	4215 Hodgkin lymphoma survivors age 18-60 (mean=35.1, SD=11.4) from prior to diagnosis through 5 years after treatment	EORTC QLQ-C30	<ul style="list-style-type: none"> Cognitive deficit was noted prior to treatment and worsened during treatment. Cognition improved somewhat after treatment but was still severely and persistently affected during survivorship. Being older and/or female associated with lower cognition. Level of cognitive deficit not influenced by treatment type. 	Small risk of bias (80%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
				<ul style="list-style-type: none">Reported correlation with psychosocial symptoms, health factors, and worse finances.	
Monteiro (2013) ³⁷	Cross-sectional survey	Age 20-39: <ul style="list-style-type: none">11 patients age 20-39 at diagnosis25 survivors age 15-39 at diagnosis435 controls	EORTC QLQ-C30, personal growth subscale of PWBS	<ul style="list-style-type: none">Patients scored significantly lower on cognitive function than controls.Survivors' scores were between those of patients and controls but did not differ significantly from either.	Limited sample, risk of biased sample and non-response bias (40%)
Nowe (2019) ³⁸	Cross-sectional survey	577 survivors age 18-39 at diagnosis	EORTC QLQ-FA12	<ul style="list-style-type: none">Higher cognitive fatigue was associated with being female, having financial problems, and having additional diseases.Breast and gynecological cancer survivors had the highest cognitive fatigue scores and testicular cancer survivors had the lowest.	None (100%)
Nugent (2018) ³⁹	Cross-sectional surveys and cognitive assessments	<ul style="list-style-type: none">23 survivors age 15-21 at diagnosis14 age- and gender-matched controls	Cognitive assessments: DVT, DSST, grooved peg board, Stroop, verbal fluency, trail-making A and B, Wechsler	<ul style="list-style-type: none">Survivors and controls showed no significant difference on the neuropsychological assessmentsSmall and medium effect sizes and direction of differences in Digit Vigilance, Stroop, work output, and perceived and total cognitive function suggest that survivors have somewhat greater difficulty than controls.Survivors reported significantly higher rate of perceived memory problems.	Risk of biased sample and non-response bias (60%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
			memory scale, letter number sequencing, Rey-Osterrieth figure, WCST PAOFI; CESD-R; WLQ	<ul style="list-style-type: none"> Significant correlation between perceived cognitive function and symptoms of depression, anxiety, and fatigue. 	
Parsons (2012) ⁴⁰	Longitudinal survey (US AYA HOPE survey)	US AYA HOPE participants age 15-39 at diagnosis: <ul style="list-style-type: none"> survey at 6-14 months post-diagnosis (n=524) survey at 15-35 months (n=465) post-diagnosis 	PedsQL	<ul style="list-style-type: none"> Over 50% reported problems at work or school at both 6-14 months and 15-35 months 35% believe treatment had a negative impact on career plans Of that 35%, 45% quit work or school completely Of participants working or in school full-time before diagnosis, at 15-34 months: <ul style="list-style-type: none"> Over 30% reported problems with “paying attention” at work/school 53% reported problems with “forgetting” 28% reported trouble “keeping up with work or studies.” 	Risk of biased sample and non-response bias (60%)
Prasad (2015) ⁴¹	Cross-sectional survey	Survivors and siblings: <ul style="list-style-type: none"> 1054 age 15-21 at diagnosis with 	BSI-18, CCSS-NCQ	<ul style="list-style-type: none"> Compared to siblings, survivors reported significantly worse task efficiency, emotion regulation, and memory, although survivors of lymphoma and sarcoma were at lower risk than other survivors. 	None (100%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
		lymphomas or sarcomas • 390 siblings		<ul style="list-style-type: none">• 21.6% of survivors had impaired memory (OR=1.44 vs. siblings)• 13.9% of survivors had impaired task efficiency (OR=1.72 vs. siblings)• Unemployment and inability to live independently were associated with reports of impaired task efficiency.	
Rey (2012) ⁴²	Cross-sectional survey and medical record review	222 breast cancer survivors in French ELLIPSE40 cohort, age 18-40 at diagnosis	Self-reported cognitive impairment, CES-D, WHOQOL-BREF	<ul style="list-style-type: none">• 21.2% of participants reported cognitive difficulties in the six months prior to diagnosis.• 37.4% of participants reported CRCI at 10 months, 36.5% at 16 months, 42.3% at 28 months.• 58.1% of women reported CRCI during at least one interview.• CRCI was associated with depression, lower quality of life, and social vulnerabilities.	None (100%)
Skoogh (2012) ⁴³	Cross-sectional survey	960 men diagnosed with testicular cancer. Age range 16-64 at diagnosis, mean=30, IQR=24-35	Questionnaire about daily behavior related to cognitive function domains: memory, attention, visuo-spatial, language,	<ul style="list-style-type: none">• More cognitive difficulties were associated with 5 or more cycles of chemotherapy, particularly in language, memory, concentration, and speed.	None (100%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
			speed, and executive		
Smith (2013) ⁴⁴	Cross-sectional survey (AYA-HOPE survey)	<ul style="list-style-type: none"> • 523 survivors age 15-39 at diagnosis • 1171 controls age 18-25 	PedsQL, SF-12	<ul style="list-style-type: none"> • Survivors age 15-17 reported worse work or school functioning than older survivors. • Higher numbers of symptoms are associated with significantly worse work/school functioning 	Risk of biased sample and non-response bias (60%)
Stadtbaeumer (2020) ⁴⁵	Longitudinal survey	3596 Hodgkin lymphoma survivors age 18-60 (mean=35.3, SD=11.4) from prior to diagnosis through 5 years after treatment	EORTC QLQ-C30	<ul style="list-style-type: none"> • Time-specific within-person improvements in cognition reduced fatigue more than vice versa. • Between-person association of lower cognitive functioning with higher fatigue. • Between-person association of higher age with lower cognitive functioning. 	Small risk of bias (80%)
Szalda (2018) ⁴⁶	Cross-sectional survey	Survivors: <ul style="list-style-type: none"> • 611 age 18-39 at diagnosis • 1742 age 40-60 at diagnosis 	Survey assessing satisfaction with and communication of survivorship care plan, and patient-reported late effects	<ul style="list-style-type: none"> • Over half (56%) of young survivors reported concerns about neurocognitive performance, although at a lower rate than older survivors. 	Limited sample, risk of biased sample and non-response bias (40%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
Trachtenberg (2018) ⁴⁷	Cross-sectional survey and cognitive assessment	51 Hodgkin lymphoma survivors age 19-48 at study, median=28	FACT-Cog, MFI-20, EORTC QLQ-C30, Cognitive assessments: BDI-II, CVLT, WAIS-III-R, TMT A+B, Stroop, Raven matrices, selected CANTAB (PAL, SOC, IED, RTI, RVP)	<ul style="list-style-type: none">Survivors scored significantly lower than healthy controls on multiple measures of cognition, primarily in executive function and memory.Survivors who had fewer chemotherapy cycles had better cognitive performance.Fatigue not associated with cognitive performance.FACT-Cog results were significantly correlated with objective cognitive performance.	None (100%)
Wefel (2014) ⁴⁸	Longitudinal cognitive assessment	53 men with NSGCT before and 12mo after treatment (Age mean=31.0, SD=7.5, range=18.5-50.7): <ul style="list-style-type: none">11 no chemo23 low chemo28 high chemo	Digit Symbol, Digit Span, TMTA, HVLT, TMTB, COWA, GPD, GPND, CES-D, STAIS	<ul style="list-style-type: none">Men receiving chemotherapy had higher rates of cognitive decline at 12 months in a dose-response pattern (0%, 52%, 67% for no, low, and high groups respectively).Most common was reduction in motor dexterity but declines in learning and memory were also common.Younger age was associated with greater decline.	Risk of biased sample (80%)
Mixed methods					

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
Armin (2019) ⁴⁹	Cross-sectional survey	<ul style="list-style-type: none"> • 3 Survivors age <15 at diagnosis • 12 survivors age 18-39 at diagnosis • 4 survivors age >39 at diagnosis 	Late effects from cancer or its treatment	<ul style="list-style-type: none"> • Cognitive changes were the most commonly reported impairment • 47% reported cognitive changes 	Little discussion of qualitative method, limited sample, risk of biased sample and non-response bias (53%)
Hauken (2017) ⁵⁰	Longitudinal rehabilitation intervention with interviews and surveys	20 survivors ages 18-35 diagnosed within prior 5 years	Interviews on treatment and rehabilitation; surveys: COPM, EORTC QLQ-C30; physical capacity measures	<ul style="list-style-type: none"> • Participants showed significant improvement in cognitive function from baseline through the rehabilitation program but did not reach the level of cognitive function of normative group. • Improvement was sustained into the follow-up period. 	Limited sample, risk of biased sample and non-response bias (80%)
Hydeman (2016) ⁵¹	Cross-sectional focus group	27 survivors age 18-39 at diagnosis and >2yr post-treatment	Concept mapping of issues important to transition to survivorship	<ul style="list-style-type: none"> • Cognitive effects of treatment were identified as an area least addressed in the transition to survivorship and one for which participants felt least prepared for in survivorship 	Limited sample, risk of biased sample and non-response bias (80%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
Vetsch (2018) ⁵²	Cross-sectional interview	42 survivors age 15-25, completed treatment within past 24 months	PAIS structured interview on vocational function in last 30 days	<ul style="list-style-type: none">• Experimenters rated cognitive or physical impairments as mild to marked for 69% of participants.• Many experienced difficulty reintegrating to school or work due to cognitive symptoms but 55% did not believe their abilities were compromised.	Limited sample, risk of sampling bias, biased sample, and non-response bias (73%)
Qualitative					
Brauer (2017) ⁵³	Cross-sectional interview	18 survivors age 15-29 at treatment, conducted 6-60 months after treatment	Perspectives on managing the return to education	<ul style="list-style-type: none">• Participants describe rushing back to school and facing overwhelming cognitive demands.• Cognitive difficulties are a barrier to successful, sustainable re-entry	None (100%)
D'Agostino (2013) ⁵⁴	Cross-sectional focus group	22 survivors age 18-35 at study stratified by age at diagnosis (≥ 18 , < 18) and diagnosis (brain cancer, other cancer)	Discussion on challenges, resources, and program recommendations	<ul style="list-style-type: none">• All age and diagnosis groups reported cognitive concerns.• All groups wanted access to neuropsychological assessment and cognitive rehabilitation.	None (100%)
Elsbernd (2018) ⁵⁵	Cross-sectional interview	9 survivors age 15-25 at diagnosis and pursuing education	Perspectives on managing the return to education	<ul style="list-style-type: none">• Participants commonly reported problems with memory and concentration.• Cognitive problems were "more difficult" to handle because they are "invisible".	None (100%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
Fauske (2019)⁵⁶	Cross-sectional interview	18 survivors of bone sarcoma ages 18-50 and 3-10yr after diagnosis at study	Psychosocial challenges in survivorship	<ul style="list-style-type: none"> • 17% reported no cognitive issues and considered themselves “back to normal”. • Other 83% reported varying degrees of cognitive effects. • Higher levels of cognitive symptoms were associated with more functional and physical difficulties and higher age. 	None (100%)
Hauken (2019)⁵⁷	Cross-sectional interview	20 survivors age 18-35, treatment completed within last 5 years	Perceived outcomes from cancer treatment	<ul style="list-style-type: none"> • All participants reported ongoing impaired function, some of whom had problems with memory and concentration. 	None (100%)
Lopez (2019)⁵⁸	Cross-sectional interview	Survivors of gynecological cancer: <ul style="list-style-type: none"> • 16 age 18-39 • 13 age 40+ 	Interviews on unmet support needs	<ul style="list-style-type: none"> • All women reported a sense of loss of some kind. • Many reported loss of role and capacity related to employment, childcare, and daily activities, usually related to treatment effects including “chemo-fog”. 	None (100%)
McLoone (2011)⁵⁹	Cross-sectional interview	<ul style="list-style-type: none"> • 19 survivors age 12-18 at diagnosis • 36 parents • 15 siblings over age 12 	Factors related to survivors' return to school after cancer treatment	<ul style="list-style-type: none"> • Half of students had difficulty concentrating in class and reduced academic performance. • Two-thirds of parents reported reduced academic performance. • Some students had difficulty with new material, especially in math. • Three-quarters of families used tutoring to help “catching up”. 	None (100%)

Article	Method	Participants	Measures	Cognitive Results / Outcomes	MMAT limitations (score)
Ruddy (2013) ⁶⁰	Cross-sectional focus group	36 female breast cancer survivors age 18-42 at study, avg of 22mo post diagnosis	Unmet needs	<ul style="list-style-type: none">• Many women reported substantial changes to memory and challenges becoming accustomed to those changes.• Women desired better resources on expected treatment effects.	None (100%)
Stevens (2018) ⁶¹	Cross-sectional survey, focus group, and interview	Survivors age >=16 at diagnosis, 16-24 at time of study, family members, professionals: <ul style="list-style-type: none">• Survey: 42 AYAs, 28 family, 54 pros• Focus group: 7 AYAs• Interview: 6 AYAs, 4 family, 97 pros	Unmet needs for AYAs	<ul style="list-style-type: none">• AYAs needed more and better support and identified a prioritized set of requirements.• 46% of patients wanted support in dealing with brain fog, but less than 5% were actually offered it• The final recommendation related to cognition is “Patients should have access to support and advice regarding the management of brain fog.”	None (100%)