

Psychological Outcomes, Health-Related Quality of Life, and Neurocognitive Functioning in Survivors of Childhood Cancer and Their Parents

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KEYWORDS

- Distress • Depression • Anxiety • Neuropsychological • Parent • Intervention
- Health-related quality of life • Posttraumatic stress

KEY POINTS

- Many childhood cancer survivors do well after treatment, but a substantial subgroup experiences psychological distress and reduced health-related quality of life. This subgroup may benefit from supportive interventions.
- Many parents report psychological distress after completion of their child's cancer treatment and years into their child's long-term survivorship. Parents experiencing distress should be offered support.

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- Neurocognitive problems are highly prevalent, particularly among survivors who received central nervous system-directed therapies. Pharmacologic and nonpharmacologic treatment approaches should be considered.
- Various interventions to help survivors and their families to cope with and adapt to the cancer experience have been developed, but there is a lack of rigorous evidence on their effectiveness and few are implemented into routine care.

INTRODUCTION

Childhood cancer is a severe disease striking children and their families unexpectedly. In developed countries, 5-year survival currently exceeds 80%¹; however, cancer remains the most common disease-related cause of death among children.² Treatment of childhood cancer can last several years and often disrupts normal developmental experiences and family home-life routines. These disruptions, in the context of disease-related events and experiences, may leave survivors and family members vulnerable to psychological distress both during and after treatment. Moreover, the effects of cancer-directed therapies may affect survivors' neurocognitive health and health-related quality of life (HRQOL) many years following the completion of treatment.

This article reviews potential psychological and neurocognitive consequences of young survivors (through 21 years of age, and who were diagnosed with cancer before the age of 18 years) and their families, as well as interventions developed to address these late effects. The authors searched PubMed for reviews on the topics of psychological distress, HRQOL, neurocognitive functioning, family/parents, and interventions in survivors of childhood cancer, and complemented these findings with studies identified by experts in the field.

PSYCHOLOGICAL HEALTH AND HEALTH-RELATED QUALITY OF LIFE***Psychological Health in Survivors***

Psychological health problems in survivors of childhood cancer encompass a variety of outcomes, including depression, anxiety, externalizing behavioral problems, and posttraumatic stress symptoms (PTSS). Psychological health also includes reference to positive outcomes such as benefit finding and posttraumatic growth (PTG; benefit finding and PTG reflect positive outcomes that can be experienced after highly stressful events, such as closer relationships and greater appreciation of life).

Two early reviews showed few psychological difficulties in young survivors of childhood cancer,^{3,4} and reported similar outcomes for childhood cancer survivors and children from the general population.⁴ Overall, these findings were confirmed in a later review showing that up to 80% to 90% of survivors are psychologically well.⁵ However, many survivors do report both negative and positive outcomes after cancer treatment.⁶ A considerable number of survivors report psychological problems, and, even if symptoms are not severe enough to warrant a clinical diagnosis, they might impair HRQOL, and many survivors benefit from support or interventions. An overview of included reviews is provided in [Table 1](#) and summarized here.

General distress: overall, reviews show that around 6% to 30% of young survivors report symptoms of psychological distress.^{5,7} Survivors report decreased positive mood and self-esteem and increased sleeping difficulties and problem behaviors,

Table 1
Reviews on psychological outcomes in survivors of childhood cancer

Study	Aim	Number of Included Studies, Type of Review	Included Survivors	Outcome Measured	Results
Bruce, ¹³ 2006	Estimate prevalence and risk factors of PTSD and PTSS in survivors of childhood cancer	<ul style="list-style-type: none"> • 7 studies on survivors • 9 studies on survivors and their parents • Narrative synthesis 	Sample sizes: <ul style="list-style-type: none"> • 23–500 survivors Inclusion criteria <ul style="list-style-type: none"> • 5 wk to 11 y after diagnosis 	PTSS and PTSD	<ul style="list-style-type: none"> • Prevalence of current PTSD ranging from 4.7%–21% • Lifetime prevalence ranging from 20.5%–35% • Prevalence of PTSS: from 0%–12.5% • Overall, prevalence of cancer-related PTSD and PTSS in childhood survivors seems higher than in the general population
Duran, ¹⁶ 2013	Examine the existing literature on PTG and the perception of benefit finding among childhood cancer survivors and their families	<ul style="list-style-type: none"> • 20 quantitative studies • 12 qualitative studies • 3 mixed studies • Narrative synthesis 	Sample size: <ul style="list-style-type: none"> • Total of 2087 childhood cancer survivors • Diagnosis of cancer at <19 y of age 	Positive effects of childhood cancer experiences	Five main themes of positive outcomes: <ol style="list-style-type: none"> 1. Making sense of cancer experience (meaning-making) 2. Appreciation of life 3. Greater self-knowledge 4. Positive attitudes toward family 5. Desire to pay back society

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Study	Aim	Number of Included Studies, Type of Review	Included Survivors	Outcome Measured	Results
Eiser et al, ³ 2000	Determine psychological consequences of surviving childhood cancer	<ul style="list-style-type: none"> • 14 studies with survivors aged ≤ 21 y • Narrative synthesis 	Sample sizes: <ul style="list-style-type: none"> • 17–130 survivors 	General mental health issues	<ul style="list-style-type: none"> • 12 studies report at least for part of outcomes similar or better (less anxious and depressed; school status, behavior, overall happiness, and satisfaction more positively rated) • 8 studies reported at least in some parts poorer outcomes in survivors (adjustment problems, poorer body image; social competence and so forth). One study reported severe PTSD symptoms in 12.5% of survivors
McDonnell et al, ⁹ 2017	Synthesize current knowledge about anxiety among adolescent survivors of pediatric cancer	<ul style="list-style-type: none"> • 24 articles • 20 quantitative studies • 1 qualitative study • 3 mixed methods • Narrative synthesis and effect sizes 	Sample sizes: <ul style="list-style-type: none"> • 18–407 survivors 	<ul style="list-style-type: none"> • Posttraumatic stress • Anxiety • Worry 	<ul style="list-style-type: none"> • Overall finding: adolescent survivors are at risk for anxiety-related distress • PTSS were common among adolescent survivors; PTSD was more likely in survivors compared with general population but less likely than in adolescents with other trauma

					<ul style="list-style-type: none"> • Anxiety: mixed results with some samples reporting more, others comparable levels with comparison peers • Worry: less worry about general symptoms such as headaches, tiredness, minor illnesses, but worries about fertility, cancer risk for their children, and disclosing illness to peers or romantic partner
Mertens & Gilleland Marchak, ⁵ 2015	Systematic review of the reported mental health outcomes in adolescent childhood cancer survivors	<ul style="list-style-type: none"> • 17 articles • Narrative synthesis 	Sample size: <ul style="list-style-type: none"> • 29–2979 survivors Inclusion criteria: <ul style="list-style-type: none"> • 11–20 y at the time of study • Diagnosed with cancer before 18 y of age • At least 1 y off therapy 	<ul style="list-style-type: none"> • Psychosocial functioning • Emotional concerns and distress • Depression • Anxiety • Posttraumatic stress 	<ul style="list-style-type: none"> • Most adolescent survivors are fine • 10%–20% of survivors consistently report various psychological difficulties • Global problems with distress and general emotional functioning were reported by 13%–29% of adolescent survivors • PTSD ranged from 8.0%–13.8%, with PTSS being higher
Michel & Vetsch, ⁷ 2015	Review the available evidence on screening for psychological distress in childhood cancer survivors	<ul style="list-style-type: none"> • 8 articles (4 articles included survivors aged <20 y only) • Narrative synthesis 	Sample sizes: <ul style="list-style-type: none"> • 32–202 survivors 	Distress measured with: <ul style="list-style-type: none"> • HUI 2 system • BYI-II • BDI-Y • SDQ 	<ul style="list-style-type: none"> • Depending on measure and outcome, between 6.2% (HUI 2, Mobility) and 22.0% (HUI 2, sensation) of adolescent survivors reported psychological distress

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Study	Aim	Number of Included Studies, Type of Review	Included Survivors	Outcome Measured	Results
Taieb et al, ¹² 2003	<ul style="list-style-type: none"> Estimate the prevalence of PTSS and/or PTSD in childhood cancer survivors Search for predictors of posttraumatic stress response 	<ul style="list-style-type: none"> 8 studies on childhood cancer survivors only 5 studies both survivors and their parents Narrative synthesis 	Sample size: <ul style="list-style-type: none"> 6–300 survivors Mean age at study 8–16 y 	PTSS and PTSD	<ul style="list-style-type: none"> Prevalence of PTSS of moderate to severe intensity or PTSD: 2%–20% of survivors Lifetime prevalence of PTSD: 20.5%–35% Two controlled studies with the largest sample sizes (N = 309 and N = 130 showed no significant differences between childhood cancer survivors and healthy control children) Predictors: <ul style="list-style-type: none"> Subjective beliefs about past and present life threat, general level of anxiety, unsatisfactory or chaotic family functioning/poor social or family support
Stam et al, ⁴ 2001	Describe emotional adjustment, including self-esteem, anxiety, depression, and posttraumatic stress	<ul style="list-style-type: none"> 40 articles Narrative synthesis 	Sample size: <ul style="list-style-type: none"> 20–309 survivors Inclusion criteria: <ul style="list-style-type: none"> Survivors aged up to 18 y 	Emotional adjustment measured with standardized instruments including: <ul style="list-style-type: none"> Self-esteem Anxiety Depression Posttraumatic stress 	<ul style="list-style-type: none"> Prevalence of psychosocial problems experienced by survivors is similar to that found in children in the general population Overall, emotional adjustment of the survivors as a group was within normal limits, not differing from that in their healthy peers

					Predictors: <ul style="list-style-type: none"> Survivors' adjustment associated with older age at diagnosis, longer time off treatment, irradiation therapy, severe medical late effects, parents and family functioning
Turner et al, ¹⁷ 2018	Review the relationship between PTG and demographic, medical, and psychosocial correlates in individuals of any age who were affected by cancer in childhood or adolescence	<ul style="list-style-type: none"> 18 studies Narrative synthesis and meta-analysis 	Sample size: <ul style="list-style-type: none"> 8730 participants in total In 10 studies all participants aged <21 y Average age at time of survey 17.92 y 	PTG	Predictors: <ul style="list-style-type: none"> Participants who were older when surveyed, or older when diagnosed with cancer, were more likely to experience PTG Less time since diagnosis and treatment completion was associated with greater PTG Small, significant, positive correlation between posttraumatic stress and PTG Greater social support and optimism were associated with greater PTG in individuals affected by childhood or adolescent cancer
Wakefield et al, ⁶ 2010	Review psychosocial functioning in children who have completed cancer treatment	<ul style="list-style-type: none"> 19 studies Narrative synthesis of quantitative studies Metaethnography of qualitative studies 	Sample sizes: <ul style="list-style-type: none"> Qualitative studies: 1–51 survivors 	Psychosocial outcomes	<ul style="list-style-type: none"> Medium to large effects for decreased positive mood and self-esteem, and increased sleeping difficulties and problem behavior

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Study	Aim	Number of Included Studies, Type of Review	Included Survivors	Outcome Measured	Results
			<ul style="list-style-type: none"> Quantitative studies: 6–161 survivors Inclusion criteria: <ul style="list-style-type: none"> Survivors diagnosed with cancer Treatment completion <5 y previously at age <18 y 		<ul style="list-style-type: none"> More anxiety than healthy children (by 2–3 y posttreatment completion anxiety seems to normalize) Smaller effects for depression, PTSD-like symptoms, learning difficulties, emotional stability, and HRQOL Positive outcomes include high levels of global self-worth, good behavioral conduct, and psychosocial hardness
Zada et al, ¹⁰ 2013	Characterize the prevalence and burden of emotional dysfunction in this population of patients/children with cranio-pharyngiomas	<ul style="list-style-type: none"> 8 studies on emotional/ affective dysfunction Calculation of a combined prevalence 	Sample size: <ul style="list-style-type: none"> Total of 146 children with cranio-pharyngiomas 	Emotional/ affective disturbances	39.7% (58 out of 146) survivors reported emotional/affective dysfunction, mainly depressive symptoms

Abbreviations: ALL, acute lymphoblastic leukemia; BDI-Y, Beck Depression Inventory for Youth; BYI-II, Beck Youth Inventory-II; HUI 2, Health Utilities Index Mark 2 system; PTSD, posttraumatic stress disorder; SDQ, strength and difficulties questionnaire.

with overall generally small to medium effects.⁶ A large study using data from almost 4000 adolescent survivors of childhood cancer participating in the Childhood Cancer Survivor Study (CCSS) showed that around two-third of survivors had no significant parent-reported behavioral, social, or emotional symptoms. However, around 16% showed increased externalizing behaviors (eg, aggressive or antisocial behavior), 9% showed increased internalizing behaviors (eg, symptoms of depression, anxiety, or social withdrawal), and 5% experienced increased global symptoms (both internalizing and externalizing) compared with siblings. Internalizing problems were especially prevalent among survivors who had been treated with cranial radiotherapy, with 31% showing these problems (although none showed externalizing problems only).⁸ Survivors of leukemia or central nervous system (CNS) tumors, survivors who were older at diagnosis, women, those self-reporting late effects, and those whose parents experienced distress were shown to be at higher risk for psychological distress.^{5,6}

Anxiety: There are mixed results regarding the experience of anxiety after childhood cancer.⁹ This finding might be caused by changes in anxiety with increasing time post-treatment. Shortly after end of treatment, survivors report experiencing more anxiety, which then decreases by 2 to 3 years posttreatment.⁶ Higher anxiety can be experienced when children are returning to school and might interfere with school-entry.⁹ Studies have also shown that social anxiety might increase with time after treatment and can be particularly associated with perceived illness impact and poor body image.⁹ Also, adolescent survivors are at particularly high risk for experiencing anxiety, rather than other forms of distress.⁹

Related to anxiety are worries. Survivors commonly report worries about relapse, disclosing their illness to peers and potential romantic partners, fertility, and potential cancer risk for their children.⁹ Worries may increase the likelihood of risky behavior (eg, alcohol consumption) and decrease positive health behavior (eg, exercise).⁹ However, many survivors also report feeling less worried about headaches, body image, being tired, minor illnesses, and dying.⁹ Risk factors for reporting more worries depend on the type of worries but include older age, female sex, diagnosis (CNS tumor, lymphoma, Wilms tumor, other tumors), risk awareness, and perceiving the illness as not being caused by chance.⁹

Depression: similar to anxiety, results are mixed with respect to the experience of depression in young survivors of childhood cancer. Some studies indicate that survivors are less depressed than peers,³ or show small effects for risk of increased depression and emotional instability.⁶ However, subgroups of survivors do seem to be at increased risk of depression. For example, 1 review of 8 studies on children with craniopharyngioma indicated that 40% of these survivors reported affective dysfunction, mainly depression.¹⁰ In addition, reports on antidepressant use among survivors generally suggest that survivors are more likely to be prescribed antidepressants than the general population, with survivors treated with stem-cell transplant and solid tumors in the extremities at highest risk.¹¹

PTSS seem to be common among adolescent survivors of childhood cancer, with a current prevalence of 2% to 20% and a lifetime prevalence of 21% to 35%.^{5,12,13} However, the prevalence is not as high as in adolescents who have experienced other forms of trauma.¹³ In contrast with other traumas, there is some indication that PTSS do not decrease with increasing time following cancer diagnosis.^{12,13} A recent study found that, although PTSS are common, posttraumatic stress disorder (PTSD) is rare in young survivors.¹⁴ Risk factors for PTSS among cancer survivors include female sex, poor family functioning, parental PTSS, experiencing late effects of treatment, relapse, anxiety, perceived life threat, and greater treatment intensity.^{9,13}

However, other studies have found that objective disease and treatment severity are not associated with experience of PTSS.^{12,13}

Many survivors also report positive outcomes such as increased sense of self-worth, good behavioral conduct, and psychosocial hardiness after childhood cancer.⁶

Posttraumatic growth (PTG)¹⁵ is a frequently reported positive outcome of childhood cancer, not only in survivors but in the family as a whole. Childhood cancer survivors often report positive outcomes related to making sense of the cancer experience (meaning making), appreciation of life, greater self-knowledge, positive attitudes toward the family, and desire to give back to society.¹⁶ In childhood cancer survivors, PTG seems to be associated with older age at diagnosis and at measurement.¹⁷ It seems that a certain developmental stage (and cognitive capacity) is necessary to experience PTG; however, with increasing time following diagnosis, there may be a decrease in the experience of PTG.¹⁷ More social support and higher optimism have been shown to be associated with higher levels of PTG.¹⁷

Psychological Outcomes in Parents of Childhood Cancer Survivors

Parents experience high levels of distress when their child is diagnosed with cancer,¹⁸ which remain increased throughout treatment.¹⁹ With increasing time after diagnosis, overall parents' distress tends to decrease, although there is a substantial subgroup of parents who experience persistent psychological distress in the long term. Reviews summarizing psychological outcomes in parents are shown in [Table 2](#).^{18,20,21} At particular risk are mothers¹⁹ and parents who experienced high levels of distress, problematic coping, and adjustment difficulties shortly after diagnosis and in early treatment.^{20,21} With end of treatment, positive feelings such as relief predominate, but at the same time uncertainty can increase.²⁰ Parents become aware about the possibility of relapse and worry about the child's health, social life, and possible infertility.^{20,21} Some report high levels of anxiety, anger, guilt, or self-blame.^{20,21}

A subgroup of parents also experience posttraumatic stress. Concurrent prevalence of PTSD is estimated at 6% to 30% and lifetime prevalence at 27% to 54%, which is higher than among parents in the general population.^{12,13,21} PTSS also seem to be more frequent in parents than in survivors¹³ and are more prevalent in mothers than in fathers.¹⁸ Additional risk factors are low social support, problems with family functioning, and prior stressful life events. Parents' subjectively experienced severity of the cancer diagnosis and treatment is associated with PTSS, whereas the objective severity is not.¹³ Also, the presence of PTSS in one partner is associated with PTSS in the other parent.¹²

Similar to survivors, parents also report psychological growth.²² Mothers report positive experiences, such as improved relationships and a change in values, whereas fathers tend not to report these experiences.^{16,21}

One recent review indicated that social support and access to psychological counseling starting after diagnosis of cancer in the child and continuing during treatment can help parents in the long term.²¹ Nonetheless, psychosocial support systems should also be available to parents in need after their child's cancer treatment completion.²³

Health-Related Quality of Life

The World Health Organization defines childhood HRQOL as "a child's goals, expectations, standards or concerns about their overall health and health-related domains."^{24,25} With a growing number of children with cancer surviving, HRQOL has gained increasing attention in pediatric oncology research. When measuring HRQOL, it is important to take into account generic versus disease-specific questionnaires,

Table 2
Reviews on psychological outcomes in parents of childhood cancer survivors

Study	Aim	Number of Included Studies, Type of Review	Included Survivors	Outcomes Measured	Results
Bruce, ¹³ 2006	Estimate prevalence and risk factors of PTSD and PTSS in survivors of childhood cancer and parents	<ul style="list-style-type: none"> • 8 studies on parents of survivors • 9 studies on survivors and their parents • Narrative synthesis 	Sample sizes: <ul style="list-style-type: none"> • 23–500 survivors • 5 wk to 11 y after diagnosis 	PTSS and PTSD	<ul style="list-style-type: none"> • Incidences of current cancer-related PTSD in parents 6.2%–25% • Lifetime prevalence of PTSD in parents: 27%–54% • Prevalence of PTSS: 9.8%–44% • Rates of PTSD and PTSS are higher than those found in the general population and also exceed those in survivors Predictors of PTSD and PTSS <ul style="list-style-type: none"> • Female gender, reduced social support and family functioning, prior stressful life events, subjective severity of event (but not objective severity)
Duran, ¹⁶ 2013	Examine the existing literature on PTG and the perception of benefit finding among childhood cancer survivors and their families	<ul style="list-style-type: none"> • 20 quantitative studies • 12 qualitative studies • 3 mixed studies • Narrative synthesis 	Sample size: <ul style="list-style-type: none"> • Total of 115 childhood cancer survivor parents (689 mothers, 341 fathers, and 85 listed only as parents) Inclusion criteria: <ul style="list-style-type: none"> • Diagnosis of cancer at <19 y of age 	<ul style="list-style-type: none"> • Positive effects of childhood cancer experiences • Positive psychological outcome or personal growth 	<ul style="list-style-type: none"> • Mothers report PTG • Fathers did not say anything about positive experiences

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Study	Aim	Number of Included Studies, Type of Review	Included Survivors	Outcomes Measured	Results
Ljungman et al, ²¹ 2014	Describe the nature and prevalence of the long-term psychological late effects of childhood cancer for parents of childhood cancer survivors and summarize factors associated with late effects	<ul style="list-style-type: none"> • 15 articles • Narrative synthesis 	Sample size: <ul style="list-style-type: none"> • 1045 in total (624 mothers and 289 fathers, some gender unknown) • Survivors 8–20 y at study (plus 1 study 25.6 y) 	Diverse measures of psychological distress: <ul style="list-style-type: none"> • General symptoms and distress • PTSS • Worry • Disease-related thoughts and feelings • Adjustment and coping • Family functioning/ marital adjustment • Positive outcomes 	<ul style="list-style-type: none"> • Psychological distress, family functioning, and coping in normal range • PTSS 21%–44% at severe level • Feelings of anger, guilt, self-blame, and fear of relapse • Worries and concerns regarding the child's health, social life, and possible infertility • Mostly no negative effects on marital relationship • Improved relationships and changed values caused by the cancer experience Predictors: <ul style="list-style-type: none"> • Coping and adjustment stronger predictors of emotional function than children's medical and disease-related variables • Childs late effect associated with parents' level of PTSS • Access to social support systems during cancer treatment may help parents emotional well-being in the long term
Pai et al, ¹⁹ 2007	Summarize and examine the impact of pediatric cancer on parent and family functioning	<ul style="list-style-type: none"> • 29 studies (13 on survivors) • Meta-analysis 	Sample sizes: <ul style="list-style-type: none"> • 10–309 participants • Average ages of children: 4–19 y 	<ul style="list-style-type: none"> • Depression • Anxiety • PTSS • Global measure of distress • Family functioning 	<ul style="list-style-type: none"> • Parental distress decreased with increasing since the diagnosis Predictors: <ul style="list-style-type: none"> • Mothers reported slightly more psychological distress than fathers up to 1 y postdiagnosis

Taieb et al, ¹² 2003	<ul style="list-style-type: none"> • Estimate the prevalence of PTSS and/or PTSD in parents of childhood cancer survivors • Search for predictors of posttraumatic stress response 	<ul style="list-style-type: none"> • 6 studies on parents only • 5 studies both survivors and their parents • Narrative synthesis 	<p>Sample sizes:</p> <ul style="list-style-type: none"> • 30–320 parents/families • Mean age at study 10–14 y 	PTSS and PTSD	<ul style="list-style-type: none"> • Prevalence of PTSS of moderate to severe intensity or PTSD: 10%–30% of parents • Lifetime prevalence of PTSD: 54% (only 1 study) • In 2 controlled studies with the largest sample sizes, both mothers and fathers of survivors reported significantly higher levels of PTSS than comparison parents <p>Predictors:</p> <ul style="list-style-type: none"> • Subjective beliefs about past and present life threat, general level of anxiety, unsatisfactory or chaotic family functioning/ poor social or family support • Presence of posttraumatic stress in one parent is associated with presence of symptoms in the other parent
Vrijmoet-Wiersma et al, ¹⁸ 2008	<p>Estimate prevalence and nature of parental strain</p>	<ul style="list-style-type: none"> • 26 studies on parents of survivors • Narrative synthesis 	<ul style="list-style-type: none"> • Survivors 6 mo to 10 y after completion of treatment • 15 mo to 13 y since diagnosis 	<ul style="list-style-type: none"> • Parental strain • Parental stress reactions • Adaptation related to caring for a child with cancer 	<ul style="list-style-type: none"> • Levels of strain decreased to almost normal levels over time in most parents, but remain persistently high in a substantial subgroup <p>Predictors:</p> <ul style="list-style-type: none"> • Depression might persist in parents who initially react with moderate to high levels of depressive symptoms • PTSS symptoms in mothers remain high; fathers' PTSS symptoms decrease • Parents with high levels of emotional strain at diagnosis

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Study	Aim	Number of Included Studies, Type of Review	Included Survivors	Outcomes Measured	Results
Wakefield et al, ²⁰ 2011	Examine the positive and negative psychosocial impacts of completing childhood cancer treatment on parents	<ul style="list-style-type: none"> • 15 articles • Narrative synthesis 	Sample size: <ul style="list-style-type: none"> • 2 families to 122 mothers and 109 fathers • Average 9 mo to 5 y after diagnosis • Survivors 8–14 y at study 	Positive and negative feelings	<ul style="list-style-type: none"> • Treatment completion entails both positive and negative feelings • Parents are generally resilient at treatment completion • Anxiety about risk of relapse can be high at end of treatment but tends to decrease with time

Abbreviations: PTG post-traumatic growth, PTSS post-traumatic stress symptoms, PTSD post-traumatic stress disorder

age-specific questionnaires with a narrow versus a wide age range, self-report versus proxy report, and paper-pencil versus online questionnaires.²⁶ The number of questionnaires being used is large, with the Pediatric Quality of Life Inventory (PedsQL) among the most often used in children,^{27,28} and questionnaires such as the Short Form-36 (SF-36)²⁹ in adults. HRQOL of survivors has mostly been examined in comparison with healthy peers or siblings.

Although results of single studies are mixed, the overall picture indicates that children experience reduced HRQOL during treatment, which then returns to normal or even improves after completion of therapy and into survivorship.^{30,31} Pediatric CNS tumor survivors experience worse HRQOL compared with both general population norms as well as survivors of other types of cancer.^{32–34} Acute lymphoblastic leukemia (ALL) survivors tend to report lower HRQOL compared with healthy controls, but better HRQOL than survivors of other cancer types.³⁵ However, some studies have shown that survivors may report better quality of life than their peers,^{30,31} which may be caused by response shift (being able to compare with a time in life when HRQOL was worse) or PTG.³⁰ It is important to monitor and discuss HRQOL, symptoms, and psychosocial functioning in daily clinical practice, which can be facilitated by portals such as the evidence-based KLIK PROM portal.³⁶

Medical factors are the most frequently studied risk factors and include characteristics of the disease (diagnosis) and treatment (intensity). Results have been mixed, but fairly consistent risk factors associated with low HRQOL in survivors include certain cancer and treatment types³⁰ and presence of medical late effects.^{27,31,35} CNS tumor survivors are at risk for poor HRQOL if they had an infratentorial tumor, cranial radiation therapy, or hydrocephalus.³⁴ CNS tumor survivors with lower intelligence quotient and behavioral problems are also at increased risk of poor HRQOL.³⁴ Among bone tumor survivors, meta-analyses showed no differences in HRQOL between patients who underwent limb-sparing surgery versus amputation.³⁷

Many determinants have been studied in relation to HRQOL, but these show conflicting results, likely because of the small number of studies per determinant and different HRQOL questionnaires used.²⁷ Just as with healthy peers, women are at higher risk for reduced HRQOL.^{27,30,37} Other risk factors include older age at diagnosis^{27,30,31,33,37} and socioeconomic disadvantage.^{27,30}

Studies have thus far rarely focused on more personal protective family and child factors,²⁷ although some positive results have been shown for positive coping or social support.³¹

Psychological Interventions for Young Childhood Cancer Survivors and Their Parents

There is an increasing focus on developing interventions to attempt to improve outcomes for families affected by childhood cancer.³⁸ **Table 3** summarizes interventions that have been trialed for young childhood cancer survivors and/or their parents.

The Surviving Cancer Competently Intervention Program (SCCIP) is the intervention that has been trialed most extensively to date. SCCIP is a family-focused intervention underpinned by cognitive-behavioral principles and family systems approaches, aiming to reduce PTSS in survivors, parents, and siblings.³⁹ The 1-day manualized SCCIP program is delivered via 4 sessions to 6 to 8 families together. One randomized trial reported that survivors who participated in SCCIP had fewer arousal symptoms than controls, whereas fathers in SCCIP experienced fewer intrusive thoughts than control fathers.⁴⁰ There were no significant effects of SCCIP on mothers or siblings, and the program did not affect anxiety for any group. A subsequent trial including families at the time of cancer diagnosis (SCCIP newly diagnosed) did not result in

Table 3
Summary of key interventions developed to support young survivors of childhood cancer and their families

Study	Intervention Details	Participants	Study Design	Main Outcome Measures	Findings
Families					
Kazak et al, ⁴⁰ 2004, United States SCCIP	1-d face-to-face family group intervention that combines CBT and family therapy approaches to enhance coping skills, reduce stress, encourage cohesion	150 families: 150 survivors (10–19 y; 51% female), 146 mothers, 106 fathers, 99 siblings (10–21 y). Survivors had completed treatment 1–12 y prior	RCT with waiting-list control. Follow-up data collected 3–5 mo after intervention	Impact of Events Scale Revised. Posttraumatic Stress Disorder Reaction Index. State-Trait Anxiety Inventory. Revised Children's Manifest Anxiety Scale	Survivors: significantly greater reduction in PTSS (especially arousal symptoms) for intervention group compared with controls. No significant differences in anxiety between conditions Family: significantly greater reduction for fathers' PTSS (particularly intrusive thoughts) scores for intervention group compared with controls. There were no significant treatment effects for PTSS in mothers or siblings. There were no significant differences in family members' anxiety between conditions.

Note: there were higher dropout rates in the intervention condition, differentially affecting participants with higher PTSS at baseline. An electronic version of SCCIP (eSCCIP) has recently been piloted

Salem et al, ⁴³ 2017, Denmark FAMOS	6 sessions grounded in family systems theory and CBT delivered in participants' homes to support families to adopt healthy coping strategies after childhood cancer	68 families: 68 survivors (mean age 3.8 y, 50% female), 68 mothers, 60 fathers, 73 siblings (mean age 6 y). Families participated after the end of intensive cancer treatment	RCT with usual care control group. Data collected at baseline, and 6 and 12 mo postintervention	Retention and attrition in the RCT. Participation and retention in the intervention Acceptability of the intervention (20 items administered 6 mo postintervention) Psychosocial outcomes data will be reported in a future article	The FAMOS intervention was considered highly feasible and acceptable. The RCT participation rate was 62%. The study achieved a high participation rate for fathers. 93% of families allocated to FAMOS completed all the parent sessions. Parents reported moderate-high satisfaction with parent and child sessions, and appreciated receiving the intervention at home. 73% of parents reported learning useful cognitive skills and 47% reported using the CBT skills postintervention
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Table 3
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Study	Intervention Details	Participants	Study Design	Main Outcome Measures	Findings
Survivors					
Maurice- Stam et al, ⁴⁴ 2009, Netherlands OK Onco program	6 session, face-to-face psychoeducational group intervention Aims to improve: <ul style="list-style-type: none"> • Information seeking about cancer • Relaxation • Social competence • Positive thinking 	11 children (5 female, aged 8–12 y) and their parents. Survivors had completed treatment 1–6 y prior	Pre-post pilot study. Data collected from survivors and parents. Follow-up data collected 0–4 wk after intervention	QOK- child, QOK parent Cognitive Control Strategies Scale Intervention also discussed qualitatively in focus groups	Information seeking/ giving (5-items): 6 children reported improvement on at least 1 item from baseline to postintervention. During focus groups, parents reported that seeking information seemed irrelevant to their children because treatment completed years prior (wanted to focus on current life) Relaxation (5-items): 5 children improved on at least 1 item. 5 children still found it difficult to relax during a visit to the doctor. 2 parents reported that the relaxation component was not effective

Social competence (7-items): results varied by item, with 6 children reporting improvement in the item "I know what I am capable of doing." However, 6 children had negative outcomes or showed no improvement for some items (eg, "With my friends I talk about disease")

Positive thinking (5-items): 5 children reported improvements on the items "I think my future looks positive" and "If I have gloomy thoughts about my disease, I know what to do to feel better." During focus groups, some parents noted that their children seemed more open after the intervention. Note: an online version of this program (Onco OK Online) has recently been piloted

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Table 3
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Study	Intervention Details	Participants	Study Design	Main Outcome Measures	Findings
Sansom- Daly et al, ⁴⁸ 2019, Australia Recapture Life	6 × 90-min online group sessions (plus 1 booster), based on CBT principles Recapture Life goals: improve quality of life, reduce distress, and facilitate healthy coping Study goals: assess acceptability, feasibility, and safety of intervention	45 AYAs aged 15–25 y (23 female, mean age = 21 y). Survivors had completed treatment within last 12 mo 19 support people (parent, partner or friend)	RCT with 3 arms: Recapture Life vs online peer-support group vs waiting list. Follow-up data collected 6 wk from beginning of intervention, 5 wk after booster, and 12 mo after last session	Feasibility: technological difficulties Acceptability: opt-in/retention rates. Perceived benefit and burden Safety: clinically concerning distress cases	Recapture Life seemed to be feasible, acceptable, and safe. Feasibility data were positive; however, technological difficulties were common (at least once in 71% of sessions). Acceptability data included a 30% opt-in rate and 87% enrollment rate. 75% of participants attended ≥5 of 6 sessions. High perceived benefit, low perceived burden. 54% of AYAs returned a clinically concerning distress screen during the program; however, none reflected acute mental health risks

Santacroce et al, ⁴⁶ 2010, United States Heros Plus	Participants received usual care plus telephone-delivered coping skills training. One-on-one 7-session telephone-delivered program covering cognitive reframing, relaxation, managing uncertainty, communication skills, and problem solving	21 AYAs aged 15–25 y (53% female, mean age 21 y) and 20 parents. Survivors were diagnosed >5 y ago and completed treatment >2 y ago	RCT (usual care control) Follow-up data collected 4 wk after intervention and 12 wk after study enrollment	Mishel Uncertainty in Illness Scale State-Trait Anxiety Inventory. Posttraumatic Stress Disorder Reaction Index Posttraumatic Growth Inventory Growth Through Uncertainty Scale	Results suggested telephone delivery was feasible. Small sample size precluded inferential statistics. Investigators suggested generally positive effects, particularly in benefit finding
Parents					
Bragadottir, ⁴⁹ 2008, Iceland	Computer-mediated support group intervention (via email so that participants can remain anonymous) to improve coping through mutual support Aimed to decrease parental anxiety, depression, somatization, and stress. Also assessed the extent to which participants received mutual support	21 parents (11 mothers and 10 fathers) of children <5 y after completing cancer treatment (mean age not reported; however, most children were <5 y old at diagnosis)	Pre-post pilot Data collected before intervention (T1), 2 mo after intervention (T2), and 4 mo later (T3)	Symptom Checklist-90 Perceived Stress Scale Perceived Mutual Support Scale	For mothers, there was a significant improvement in depression from T2 to T3. For fathers, there was a significant improvement in anxiety from T1 to T3. For fathers, there was a significant improvement in perceived stress from T2 to T3 For mothers, helpfulness, altruism, instillation of hope, and universality were the strongest indicators of mutual support. For fathers, instillation of hope, universality, helpfulness, and group cohesion were strongest indicators of mutual support

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Table 3
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Study	Intervention Details	Participants	Study Design	Main Outcome Measures	Findings
					Mothers used the intervention more than fathers. Most fathers did not write messages for other parents during the intervention
Wakefield et al, ⁵⁰ 2016, Australia Cascade	3 × 120-min online group sessions delivered online. Grounded in CBT principles, as well as family systems approaches. Cascade goals: improve quality of life, reduce distress and facilitate healthy coping. Trial assessed feasibility and acceptability of Cascade and early efficacy	47 parents (39 mothers) of children aged 2–16 y were randomized to Cascade (n = 25) or a 6-mo waiting list (n = 22). Survivors had completed cancer treatment within the last 5 y	Randomized controlled trial (waiting-list control). Parents completed questionnaire at baseline, 1–2 wk, and 6 mo after intervention	Feasibility: response and attrition rates Acceptability: California Psychotherapy Alliance Scale Youth Satisfaction Questionnaire Outcomes: Quality of Life Family Caregiver Tool. Depression Anxiety Stress Scale. McMaster Family Assessment Device	Cascade seemed feasible and acceptable. Response rate was 54%, 96% of parents remained engaged across sessions, 80% completed every questionnaire. 40% of parents thought the number of sessions was appropriate, 37% desired more sessions. 70% of parents indicated that Cascade was quite or very beneficial, no parent rated Cascade as very or quite burdensome.

6 parents noted that Cascade was time consuming but the benefits outweighed the costs. There was no significant main effect of group (waiting list vs intervention) or time (baseline vs 1–2 wk postintervention vs 6 mo follow-up) on quality of life, psychological functioning, or family functioning. Fear of cancer recurrence was significantly lower at follow-up for both groups.

Abbreviations: AYA, adolescent and young adult; Cascade, Cope, adapt, survive, life after cancer; CBT, cognitive behavior therapy; FAMOS, Family-oriented Support; QOK, Questionnaire Op Koers; RCT, randomized controlled trial; SCCIP, Surviving Cancer Competently Intervention Program.

significant differences in the measured outcomes.⁴¹ An e-health version of SCCIP has recently been piloted, suggesting that eSCCIP may be acceptable, feasible, and usable.⁴²

Also focused on provision of psychosocial support to whole families is the more recent Family-oriented Support (FAMOS) intervention.⁴³ The 6-module intervention is delivered in families' homes, which may have enabled a large number of fathers (60 fathers from 68 families) to participate in a randomized controlled trial (RCT). The FAMOS feasibility and acceptability data are promising, with most invited families agreeing to participate and 93% of parents completing all FAMOS sessions. Evaluation revealed largely positive acceptability data, with parents also reporting that they learnt useful cognitive skills (73%) and that they used cognitive behavior therapy (CBT) skills since completing the intervention (47%).⁴³ Psychosocial outcomes data are forthcoming.

Three interventions have focused on survivors directly, rather than whole families. The 6-session OK Onco program is designed to improve information seeking, relaxation, social competence, and positive thinking.⁴⁴ The pilot reported positive outcomes, particularly on social competence and positive thinking. Qualitative focus group data suggested that the intervention was appropriate for young survivors. A pilot of an on-line version (OK Onco Online) reported high levels of satisfaction and low dropout rate.⁴⁵ Focusing on survivors in the adolescent and young adult (AYA) age range, Heros Plus⁴⁶ offered AYAs 7 30-minute telephone sessions to develop skills to cope with uncertainty in illness. An RCT reported promising findings (particularly for benefit finding), although the small sample size precluded significance testing. A recent 3-arm randomized trial⁴⁷ of the online Recapture Life program reported that Recapture Life was acceptable to survivors, feasible to deliver, and did not increase participants' distress across the 6-week program.⁴⁸

In addition, 2 interventions have focused on delivering psychological support directly to parents to improve coping skills and reduce distress. In Iceland, Bragadottir⁴⁹ offered a 4-month computer-mediated support group intervention, reporting declines over time in mothers' depression and fathers' anxiety symptoms. Fathers also experienced an improvement in perceived stress over time. In Australia, Wakefield and colleagues⁵⁰ offered parents an online group videoconferencing intervention (Cascade [cope, adapt, survive, life after cancer]), reporting that the intervention was feasible to deliver and acceptable to parents. However, there were no significant differences in quality of life between parents who participated in Cascade compared with wait-listed parents immediately postintervention or after 6 months. An enhanced version of Cascade is currently being assessed in a 3-arm RCT.⁵¹

Although the data discussed earlier seem promising, they are not conclusive with regard to effectiveness. Reported effect sizes are typically small and several interventions have not reported significant effects on any measured outcomes. There may be several factors driving the modest findings reported to date. Most trials recruited small samples^{44,46,48–50} or did not use a control group.^{44,49} Interventions included heterogeneous groups (eg, survivors with all types of tumors) and did not prescreen participants for existing distress. Given the emerging evidence that tailored interventions for more distressed participants can yield stronger effects than standardized interventions,⁵² there is a clear need to evaluate tailored interventions for patients most at risk. It is also possible that current trials have not selected the most appropriate outcome variables, suggesting a need to adopt measures that sensitively assess clinically important outcomes.⁵² There are also several other trials, not included in this review, that used marginally different eligibility criteria,^{53,54} related domains such as social skills,^{55,56} health knowledge/perceptions,⁵⁷ or sleep,^{58,59} or included families of children with chronic illness.^{60–62}

There are multiple opportunities to improve future intervention trials. Conducting larger studies using more standardized intervention approaches and research designs would enable pooling of results to test effectiveness more rigorously.⁶³ There is a lack of evidence regarding whether psychological interventions can achieve long-term change for this population, with most studies to date focusing on short-term impacts (with the exception of FAMOS⁴³ and Recapture Life⁵⁰). There is also a need to consider how best to provide support for men, especially fathers, who are currently underrepresented in research studies.^{40,50} As e-health interventions become increasingly prevalent, future studies need to carefully consider the potential benefits and challenges of delivering on-line psychological support to families of childhood cancer survivors.⁶³ In addition, to date, few (if any) interventions have been successfully integrated into routine clinical care. An ongoing challenge will be to identify sustainable strategies to enable interventions to continue to be offered to families into the long term.

NEUROCOGNITIVE FUNCTIONING

Neurocognitive Problems

Survivors of childhood cancer are at risk for developing neurocognitive impairments secondary to their disease and treatment. Although prevalence estimates vary across studies, more than 35% of survivors may experience neurocognitive late effects.⁶⁴ Survivors of CNS tumors are at the greatest risk of developing neurocognitive impairments.⁶⁵ Beyond deficits in general intelligence, impairments are often observed in processing speed, executive functions (eg, verbal fluency, cognitive flexibility), memory, and attention.^{64,66,67} The most salient risk factors for impairment in CNS tumor survivors include higher dose of cranial radiation therapy (CRT), larger brain volume irradiated, and younger age at diagnosis.⁶⁵ In addition, female sex, obstructive hydrocephalus, posterior fossa syndrome, and seizures have been identified as risk factors for neurocognitive impairment.^{64,65} The risk of impairment following CRT often increases in a dose-dependent manner; however, younger age at CRT remains the most important risk factor even at a lower CRT dose.⁶⁷ Importantly, advances in CRT techniques have resulted in significant dose and target volume reductions to healthy brain tissue and have been shown to reduce neurocognitive morbidities.^{66,68,69} Proton CRT minimizes dose exposure to normal brain tissue, and early studies suggest improved outcomes following treatment with proton CRT,^{70–73} although long-term follow-up data are needed.

Increased rates of neurocognitive impairment also have been reported in survivors of childhood leukemia.^{65,74} Historically, CRT prophylaxis was a critical component of curative therapy for ALL and was strongly associated with neurocognitive impairment, with higher doses of CRT conferring greater risk for poorer outcomes.⁷⁴ Contemporary treatment protocols, which consist of intensified intravenous and intrathecal chemotherapies (ie, methotrexate, cytarabine) for standard-risk patients, have resulted in reduced neurocognitive morbidities.^{65,75,76} However, survivors of ALL remain at heightened risk for neurocognitive impairment compared with population norms and healthy controls.^{75,77} Risk factors include female sex, younger age at diagnosis, and longer time since diagnosis.⁶⁵ Among survivors treated with chemotherapy only, longitudinal data suggest that many ALL survivors develop attention problems by the end of therapy^{78,79} and present with executive dysfunction and processing speed deficits more than 5 years after diagnosis.⁷⁸

Neurocognitive impairments can have a significant impact on educational and functional outcomes for survivors.⁸⁰ A recent meta-analysis reported that childhood cancer survivors are significantly less likely to complete secondary or tertiary level

education compared with their classmates without cancer and more likely to require special education services.⁸¹ Moreover, among survivors of ALL and CNS tumors, neurocognitive deficits have been associated with reduced rates of college graduation, employment, and independent living in adulthood.^{66,75}

Interventions for Neurocognitive Problems

Educational accommodations are among the most routinely provided interventions to survivors of childhood cancer. Common accommodations provided in the classroom include shortened or modified assignments, extended test-taking time, copies of class notes, modified seating within the classroom, and specialized instruction.⁶⁵ Researchers have investigated several targeted treatment approaches focused on the remediation of specific neurocognitive deficits. Early pharmacologic studies investigated the short-term and long-term efficacy of the psychostimulant methylphenidate in survivors of CNS tumors and ALL.^{82,83} In 1 study, methylphenidate was associated with improved attention and social skills in survivors, but similar gains in academic performance were not observed.⁸² A 24-week trial of the acetylcholinesterase inhibitor donepezil was associated with improvements in executive functioning and visual memory in brain tumor survivors.⁸⁴ Promising nonpharmacologic intervention approaches have included home-based computerized cognitive training such as Cogmed.^{85–87} Improvements have been observed in the cognitive skills targeted by the interventions (eg, working memory), with maintenance of gains observed at 6-months after the intervention.⁸⁷ More recently, investigators have examined the impact of physical activity interventions on neurocognitive functioning in childhood cancer survivors. A 12-week group-based exercise intervention was associated with improved reaction time and increased white matter and hippocampal volume in brain tumor survivors,⁸⁸ whereas a 24-week Web-based physical activity intervention was associated with improved inhibitory control in a heterogeneous group of survivors; however, the observed improvement was not maintained at a 6-month follow-up.⁸⁹ In contrast, a recent examination of neurofeedback in brain tumor survivors did not show positive effects on attention, memory, processing speed, or executive function.⁹⁰

SUMMARY

Despite largely positive outcomes for survivors of childhood cancer and their families, there remains a substantial group who have psychological, HRQOL-related, and neurocognitive problems. If untreated, these problems can persist into adulthood and very-long-term survivorship.⁹¹ Several interventions have been developed and tested, with promising findings reported in pilot studies and small-scale RCTs. There is a critical need to offer survivors and their families targeted support, starting with the diagnosis of cancer and continuing through treatment and into survivorship. Recently published psychosocial standards of care for childhood cancer survivors⁹² can be used as a framework to implement and evaluate the efficacy of interventions in the future.

DISCLOSURE

The authors have nothing to disclose.

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