Childhood Cancer Survivorship: Daily Challenges

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KEYWORDS

• Fatigue • Pain • Physical activity • Health behaviors • Social adjustment • Survivorship

KEY POINTS

- Survivors of childhood cancer are at elevated risk of experiencing fatigue, pain, decreased physical activity, engagement in risky health behavior, and poor social adjustment.
- Risks are more pronounced for survivors of specific diagnoses or those receiving specific treatment protocols (eg, survivors of central nervous system (CNS) tumors or receiving CNS-directed therapies).
- Interventions to address these outcomes are in their infancy.
- Future research should focus on exploring the antecedents and consequences of these outcomes.

BACKGROUND

Survivors of childhood cancer have an elevated lifelong risk of developing chronic health problems or late effects. These negative effects encompass physical, psychological, social, and cognitive domains and include fatigue, pain, lifestyle (ie, decreased physical activity, engagement in risky health behaviors), and poor social adjustment.[1–4] The prevalence of late effects among survivors of childhood cancer is

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staggering: 95% will be diagnosed with at least one chronic health condition by the age of 45 years; 80.5% will be diagnosed with a disabling or life-threatening condition.[5] Many of these late effects have severe consequences that can lead to premature mortality and long-term morbidity.[6] The adoption of a variety of health behaviors may attenuate or exacerbate some of the health problems.

Knowledge related to the late effects in survivors of childhood cancer is also evolving, as research dedicated to this field becomes more sophisticated in its methodology. Specifically, research related to outcomes including fatigue, pain, lifestyle behaviors, and social adjustment after treatment have benefited from studies that have included larger sample sizes, more robust approaches to measurement, and greater specificity with respect to populations sampled (eg, focus on specific diagnosis or treatment protocol).

The goal of this review is to examine the state of the recent literature with respect to fatigue, pain, lifestyle behaviors, and social adjustment among survivors of childhood cancer and identify directions for future research. For each outcome the following questions were asked: what is the problem, who is at risk, and what can be done about it? Specifically, the authors sought to determine the prevalence of each outcome, the risk factors associated with each outcome, and finally whether there are interventions that exist to help remediate problems.

METHODS

A comprehensive literature search was completed using the following databases: PubMed, PsycINFO, SPORTDiscus, and EMBASE, using search terms listed in **Table 1**. Articles were reviewed independently by study authors (FS, CF, AW, MP) using the following inclusion criteria: (1) published in English; (2) included children diagnosed with cancer between 0 and 21 years of age; (3) described survivors 5 years from diagnosis and/or 2 years from therapy completion; and (4) were original studies. In addition, articles had to be published between 2014 and December 3, 2019. Separate reviews were conducted for each outcome examined (ie, fatigue, pain, physical activity, lifestyle behaviors, social adjustment).

RESULTS

Across the 5 different outcomes examined, a total of 11,545 articles were retrieved (Fatigue $n = 705$; Pain $n = 429$; Physical Activity $n = 1730$; Lifestyle Behaviors $n = 3032$; Social adjustment $n = 5649$). Articles were scanned at the title/abstract level and ultimately 333 were retained for inclusion in the current review (Fatigue $n = 30$; Pain $n = 21$; Physical Activity $n = 150$; Lifestyle behaviors $n = 45$; Social adjustment $n = 87$). What follows is a narrative summary of the state of the literature with regard to fatigue, pain, physical activity, lifestyle behaviors, and social adjustment.

Fatigue

The Canadian Cancer Society defines fatigue as “a general lack of energy, tiredness or exhaustion. It is different from the tiredness a person usually feels at the end of the day. Fatigue is not necessarily related to activity and may not go away with additional rest or sleep”.[7] Fatigue is conceptualized to be a multifactorial product of physiologic (eg, circadian rhythms, metabolic status), physical (eg, physical activity level, disease and treatment factors, comorbid symptoms and conditions), and psychosocial (eg, behavior, mental-health variables, demographic variables) determinants.[8,9] Although limited, there is conflicting evidence regarding the prevalence of fatigue between survivors of childhood cancers and controls, with recent reports indicating a prevalence

Table 1
Search terms used

Search Category	Terms Used
Outcome	
Fatigue	Fatigue[ti]
Pain	Pain[ti]
Physical Activity	"physical activity"[ti] OR exercise[mh]
Lifestyle	alcohol OR smoking OR sun protection OR tobacco OR Marijuana OR illicit [Title/Abstract]))
Social Adjustment	"social behavior"[mh:noexp] OR "social skills"[mh] OR "social skills"[tiab] OR relationship*[tiab] OR social[ti])) relations[ti] OR relationship*[ti] OR conflict*[ti])) OR "independent living"[mh] OR "independent living"[tiab] OR income OR marital[ti] OR marriage[ti] OR unmarried[tiab] OR (social[ti] AND support[ti]) OR job[ti] OR vocation[ti]
Population	child[mh] OR child[ti] OR children*[ti] OR kids[ti] OR youth[ti] OR juvenile[ti] OR pediatric*[ti] OR pediatric*[ti] OR infant[mh] OR infant*[ti] OR infancy [ti] OR schoolchildren[ti] OR childhood[ti] OR preschooler*[ti] OR girls[ti] OR boys[ti] OR adolescen*[ti] OR adolescent[mh] OR teen[ti] OR teens[ti] OR teenager*[ti]
Problem	neoplasms[mh] OR neoplas*[tiab] OR cancer*[tw] OR tumor*[tiab] OR tumor*[tiab] OR carcinoma*[tiab] OR malignan*[tiab] OR oncolog*[tiab] OR oncolog*[jour] OR metasta*[tiab] OR leukemia*[tiab] OR lymphoma* [tiab] OR hodgkin[tiab] OR hodgkin*[tiab] OR T-cell[tiab] OR B-cell[tiab] OR non-hodgkin[tiab] OR sarcoma[tiab] OR sarcom*[tiab] OR sarcoma [tiab] Ewing's[tiab] OR Ewing*[tiab] OR osteosarcoma[tiab] OR osteosarcom*[tiab] OR "wilms tumor"[tiab] OR wilms*[tiab] OR nephroblastom*[tiab] OR neuroblastoma[tiab] OR neuroblastom*[tiab] OR rhabdomyosarcoma[tiab] OR rhabdomyosarcom*[tiab] OR teratoma [tiab] OR teratom*[tiab] OR hepatoma[tiab] OR hepatom*[tiab] OR hepatoblastoma[tiab] OR hepatoblastom*[tiab] OR PNET[tiab] OR medulloblastoma[tiab] OR medulloblastom*[tiab] OR PNET*[tiab] OR "neuroectodermal tumors"[tiab] OR retinoblastoma[tiab] OR retinoblastom*[tiab] OR meningioma[tiab] OR meningiom*[tiab] OR glioma[tiab] OR gliom* OR "brain cancer"[tiab] OR (brain[ti] AND (cancer* [ti] OR neoplasm*[ti])) OR brain tumor*[tiab] OR brain tumor*[tiab] OR "posterior fossa syndrome"[tiab]

ranging from 13.8%, an average of 13.1 years, posttreatment to 48.4%.[10,11] Although some studies suggest that survivors of any childhood cancer have significantly worse fatigue than controls or population norms,[11–14] others have found no significant differences across heterogeneous samples of cancer survivors or among specific diagnoses.[10,15] One possible explanation for these disjointed findings is that this literature continues to be plagued by widely differing methodologies. Fatigue scales used within the literature vary widely or have simply determined the presence of fatigue based on a single yes/no question.[12,16] Moreover, this literature has almost exclusively included samples of survivors of childhood cancers with heterogeneous diagnoses, complicated by varying treatment protocols. Further, research in this area has evaluated survivors of childhood cancers aged anywhere from 10 to greater than 30 years posttreatment together in analyses, potentially clouding findings.

There is consistency within the literature with respect to the factors related to increased fatigue among survivors of childhood cancer. Specifically, fatigue

has been found to be related to greater emotional distress, including depression, and lower quality of life. Emerging research also links fatigue to pain.[10,14,15,17,18] Limited evidence also suggests that fatigue in survivors of childhood cancer is related to neurocognitive functioning, particularly among female survivors.[19] Unfortunately, given the largely observational nature of these studies, directionality of these relationships cannot be determined. More longitudinal research exploring fatigue over time would help clarify potential mechanisms and associations.

Interventions

The last 5 years has seen a growth in the development of interventions to combat fatigue in survivors of childhood cancer. One innovative study examined the use of cognitive behavior therapy for treatment of fatigue with moderately successful findings.[20] Physical activity interventions have also been identified as successful therapies for fatigue.[21] These interventions are discussed later in greater detail.

Pain

Pain has become of increased interest in more recent literature related to survivors of childhood cancer. Among the few studies that investigated chronic pain, the prevalence is estimated to be between 11% and 56%.[22,23] Although, only one study[22] explored chronic pain using a valid definition of pain lasting 3 months or longer. Similar to the methodological limitations that plague the research on fatigue, pain is typically measured using items derived from health-related quality-of-life questionnaires or created by the investigators. Both options only use 1 or 2 items to capture pain, which is a cause for concern because pain is a complex, multidimensional construct that includes intensity, frequency, duration, chronicity, interference, and affect, all of which cannot be captured in 1 or 2 items. Future research should reference the chronic noncancer pain literature to better capture multiple dimensions of pain in this unique population using validated, theoretically grounded measures of pain. Moreover, longitudinal are needed to reliably assess the chronicity and duration of pain.

Certain disease and treatment factors may put individuals at risk for experiencing pain in survivorship. Evidence suggests that survivors of high-risk acute lymphoblastic leukemia,[24] bone tumors,[13,24] and soft tissue sarcomas[13] may experience more pain than those of children with other cancer diagnoses. Survivors may be at increased risk of experiencing pain if they have a history of total knee replacement surgery,[25] radiation,[26] disease recurrence,[26] or posttreatment meningioma.[27] Finally, there is evidence to suggest that high-risk neuroblastoma survivors who underwent hematopoietic stem cell transplantation also experience pain in survivorship.[27] There is consistent evidence to suggest that female survivors report more pain than male survivors,[23,26,28] but there is conflicting evidence for the relationship between age at diagnosis and pain as well as current age and pain.

Pain in survivors of childhood cancer is associated with a myriad of poor psychosocial outcomes. Survivors with pain are more likely to report increased fatigue,[13,15,23,29] daytime sleepiness,[15] psychological distress,[30,31] anxiety,[31] and depression.[31] Pain in survivors of childhood cancer is also generally related to diminished health-related quality of life.[26,32,33] In terms of social factors, there is evidence to suggest that pain is related to lower socioeconomic status.[31] Based on the current literature, the directionality of the association between pain and psychosocial outcomes is unclear in that there is not enough evidence to suggest causal relationships. More longitudinal research exploring pain over time would help clarify this.

Interventions

To date, no pain management interventions exist for survivors of childhood cancer, despite the literature suggesting that many survivors experience pain after their treatment has completed. Psychological treatment of the management of chronic pain in noncancer populations aims to reduce disability due to pain, but research on these treatments has not been extended to survivors of childhood cancer. Researchers are encouraged to draw from the chronic noncancer pain intervention literature to test the feasibility, acceptability, and efficacy of these interventions on survivors.

Lifestyle After Treatment

Protective behavior

Physical activity One lifestyle behavior that can improve health among survivors of childhood cancer is physical activity. Physical activity has been defined as any bodily movement resulting in increased energy expenditure above resting level, whereas exercise is a subset of physical activity that is planned, structured, and repetitive.[34] For the purpose of this overview of the literature, the broader term "physical activity" is used throughout.

Research has demonstrated that physical activity levels typically decrease during treatment and often remain low thereafter.[35] As a result, childhood cancer survivors engage in physical activity at similar or lower rates than their peers without a history of cancer.[36–41] The reason for the low rates of physical activity among childhood cancer survivors may be related to a range of influencing factors. Indeed, physical activity among childhood cancer survivors may be influenced by personal (eg, past experience, competing demands), physical (eg, fatigue, fitness levels), psychological (eg, fear of injury, self-confidence, and self-esteem), medical (eg, physical limitations), social (eg, parental attitudes toward physical activity), cognitive (eg, developmental status), and environmental factors (eg, lack of programs/opportunities).[42–44]

Benefits of physical activity There are numerous observational studies examining beneficial relationships between participating in physical activity and greater physical, psychological, social, and cognitive outcomes in survivors of childhood cancer.[37,45–47] Further, researchers have found that physical activity is positively associated with improved cardiopulmonary functioning[48] and better cardiovascular profiles (ie, lower fat mass and greater lean muscle mass).[49,50] This is seen even among childhood cancer survivors who were treated with cardiotoxic agents[51] such as anthracyclines.[52] Higher levels of rigorous-intensity physical activity has also been associated with a lower risk of cardiovascular events in a dose-dependent manner among survivors of Hodgkin lymphoma[53] and lower all-cause mortality in a sample composed of mixed cancer survivors.[54]

The evidence linking physical activity to health benefits in survivors is primarily from cross-sectional studies with leukemia and lymphoma survivors or mixed samples with limited representation from other types of cancer (eg, brain tumor, bone tumor). Thus, evidence for whether higher levels of physical activity improves physical, psychological, social, and cognitive outcomes over time, and the ways in which these relationships may differ across subgroups, remains unclear. In addition, a relatively narrow range of psychological and social outcomes (eg, self-esteem, social support) have been explored across studies and interactions between studied variables have rarely been examined. This gap in knowledge leaves questions regarding potential mediators and moderators and the processes through which physical activity exerts its beneficial effects unanswered. For those seeking to understand the relationships between physical activity and physical, psychological, social, and cognitive outcomes, biobehavioral

models may be a useful starting place to guide variable selection. Although several avenues for future research remain, collectively, the published evidence suggests that higher physical activity is associated with a range of positive effects.

Interventions Experimental studies show that physical activity interventions are safe, feasible, and beneficial in children after treatment of cancer.[55–60] Among childhood cancer survivors, a range of benefits have been documented covering behavioral, physical, psychological, and social outcomes.[21,61–69] Specifically, researchers have reported improved physical health (eg, reduced cancer-related fatigue, improved body composition, physical fitness, and coordination), psychological health (eg, greater self-efficacy, positive mood, and quality of life), and social well-being (eg, fostering feelings of social support).[21,61–69] Although there is some variability in these effects, positive outcomes are observed across interventions that range in duration and intensity from giving childhood cancer survivors physical activity equipment (eg, bike,[61] Fitbit[64]), to a 4-day adventure training program,[21,62] to a 12-week physical activity intervention, composed of 2 to 3 weekly supervised sessions, lasting for 30 to 90 minutes.[66] There is also early evidence to suggest that physical activity has a positive impact on some of the common cancer-related complications children face following treatment. Specifically, physical activity may improve neurocognitive function (eg, cortical thickness, reaction time)[70–72] and alleviate symptoms of cardiac toxicity.[73,74] Bone mineral density has also been shown to improve with low-magnitude, high-frequency mechanical stimulation (which may mimic some aspects of physical activity).[75]

Notwithstanding the benefits reported and contributions made by the studies described earlier, there remain important gaps in knowledge. There is variability in terms of intervention designs and measures used. This precludes the ability to pool data and draw robust conclusions. More research is needed to provide insight into the effects of physical activity on a broader range of outcomes relevant to childhood cancer survivors (eg, self-esteem). Adherence to physical activity interventions can also be challenging, with some researchers reporting adherence as low as 25%.[60] Delineating whether nonsignificant and/or mixed effects are due to poor adherence, inadequate physical activity doses, or other reasons is therefore difficult. Although adherence is typically highest within supervised interventions, home-based intervention techniques are often preferable with this population due to pragmatic considerations (eg, small, geographically spread out population). Exploring strategies to promote behavior change outside of a supervised intervention by incorporating behavior change techniques (eg, goal setting, action planning)[76] may be one way to facilitate adherence within home-based interventions in this population.

Risky behavior

Smoking Recent evidence suggests that survivors of childhood cancer smoke at rates ranging from 9.1% to 34.6%.[77,78] Although most of the studies found that survivors smoke at rates lower than the general population or control groups,[79–82] some find survivors smoke at the same rate,[36,83] or even higher rates than controls.[78,84,85] Among large cohort studies, the St. Jude Lifetime Cohort Study (SJLIFE) found that 24.9% of survivors of childhood cancer smoked compared with 28.3% in control group,[86] whereas the Childhood Cancer Survivor Study (CCSS) reported 14.3% of survivors of childhood cancer smoked versus 21.3% in sibling controls,[87] and the British Childhood Cancer Survivor Survey (BCCSS) found that survivors of childhood cancer smoked less frequently than British population norms.[79,88] A meta-analysis by Marjerrison and colleagues[82] found the frequency of survivors of childhood cancer

who smoke was 22% and survivors of childhood cancer were less likely to smoke compared with siblings and healthy controls.

It is of course encouraging that survivors generally smoke less frequently than the general population. However, it remains concerning that any survivors smoke given the additive health risks associated with smoking in this population. Smoking in the general population has been linked to significant health problems including pulmonary dysfunction and cancer. In fact, cardiac and pulmonary dysfunction are among the most common late effects experienced by survivors of childhood cancer (56.4% and 65.2%, respectively).[89] Smoking in this medically vulnerable population has been associated with poorer mental health and physical health[90] including peripheral neuropathy[86] and decreased bone marrow density (BMD), which may put survivors at risk of osteoporosis and bone fractures.[91,92] Oancea and colleagues[93] found decline in pulmonary function in a young cohort of survivors of childhood cancer (median age 35 years) with a history of smoking. Former smokers (median 10 years from quitting) who reported smoking approximately 4.5 packs of cigarettes per day mirrored the pulmonary function of individuals in the general population who smoked 10 packs per day. This study shows that young survivors of childhood cancer are at risk of lung disease even with moderate levels of smoking. Treatment factors such as radiation makes survivors with a history of smoking particularly vulnerable for adverse health outcomes such as lung cancer[82] and increased risk of miscarriage.[94]

Perhaps equally concerning is evidence that survivors of childhood cancer underreport their smoking status in research studies. Huang and colleagues found that 37% of survivors of childhood cancer who reported that they were former smokers were currently smoking when their status was verified by bioanalysis. In addition, 7% of those who reported never smoking were found to be smokers. Misclassification of smoking status was related to younger age, male sex, and current marijuana use.[95]

Longitudinal data from the CCSS found that older age at diagnosis was associated with increased risk of any history of smoking.[80] Treatment factors such as receiving therapy toxic to the lungs or heart was not associated with smoking. Survivors who currently had one or more chronic health problem were also equally likely to smoke. Rates of smoking increased with age[96] and having peers who smoke[81]; however, survivors were more likely to delay initiation of smoking compared with peers.[36]

Alcohol use Rates of alcohol consumption in survivors of childhood cancer are difficult to characterize because of the various reporting methods. Some studies report on percentage of survivors who currently drink alcohol, whereas others report on the number of alcoholic units or drinks per week. Other studies classify drinking habits as being risky or binge drinking. Many studies indicate a similar percentage of drinking or binge drinking among survivors of childhood cancer,[36,84,97,98] whereas other studies report a lower percentage compared with siblings and healthy controls.[79,86,88,99] A meta-analysis by Marjerrison and colleagues[82] found 20% of survivors were binge drinking, which was lower compared with siblings but similar to healthy controls.

Young adult survivors may be particularly prone to risky drinking. Among leukemia survivors in the SJLIFE cohort, 43% reported risky drinking behavior classified as men taking more than 4 drinks per day or more than 14 drinks per week or women who take more than 3 drinks per day or more than 7 drinks per week. Cantrel and Posner[84] also reported more young adult survivors of childhood cancer binge drinking (43.3%) among the National Longitudinal Study of Adolescent Health. Using criteria from the *Diagnostic and Statistical Manual of Mental Disorders, 4*th *Edition*, 72.2% had at least one alcohol abuse symptom, whereas 51.1% were classified as having severe alcohol

abuse symptoms. A French study by Bagur and colleagues[100] similarly found a high level of risky drinking in young adult male survivors who were more likely to have an alcohol dependence or abuse problem compared with men in the general French population (19.6% vs 9.4%).

Despite high levels of problem drinking in young adult survivors, it seems that survivors of childhood cancer begin drinking later than their peers.[36,77,101] This delayed onset of alcohol use may be attributed to delayed socialization or parent protectiveness following cancer treatment[77] but it may provide health care providers with an opportunity to engage young patients in conversations about alcohol use and healthy lifestyle choices.

Drinking alcohol before 18 years of age was related to a 30% increase in memory impairment, 30% increase in risk of depression, and 60% increase in risk of anxiety.[101] Risky drinking has been associated with frailty in survivors of leukemia,[92] and binge drinking has been associated with increased emotional distress.[101] Even a moderate level of alcohol consumption has been linked to decreased BMD.[92]

Drug use Street drug use in survivors of childhood cancer has not been well characterized. A meta-analysis by Marjerrison and colleagues[82] found only 7 articles reporting rates of drug use in survivors of childhood cancer. Overall, drug use was 15% in survivors of childhood cancer, which was less than that in matched controls. Several studies have attempted to capture cannabis use in this population. The reported use of cannabis in survivors of childhood cancer varies widely from 8%[97] to 53%.[100]

In adolescent and young adult survivors of childhood cancer, risk of cannabis use increased with age.[96,100] In a cohort of young survivors of childhood cancer in the United States, increased depressive symptoms, male sex, and higher socioeconomic status were associated with increased marijuana use.[96]

Multiple substance use Nearly 50% of the general population engages in multiple risky health behaviors such as alcohol use, smoking cigarettes, and drug use.[99] Co-occurring risky health behaviors can compound health problems that put survivors of childhood cancer at particularly high risk.[99] For example, adolescents from the CCSS who reported binge drinking, marijuana use, and smoking cigarettes were more likely to engage in risky sexual behavior including unsafe sex and early initiation of sexual activity.[102] Milam and colleagues[96] found that 16% of adolescent and young adult (AYA) survivors of childhood cancer used multiple risky substances (drinking, smoking, and/or marijuana), whereas Lowe and colleagues[103] reported that 24% of AYA survivors engaged in multiple risky behaviors. In a study by Huang and colleagues[95] examining smoking habits in adult survivors of childhood cancer, 81% of self-identified smokers also reported using marijuana.

Clinical factors such as age at diagnosis and cancer type are not related to substance use[96]; however, increased age for AYAs[104] and psychological distress[96,99,103] predict multiple substance use.

Interventions Given the serious health impacts of risky health behaviors in survivors of childhood cancer, early and continuous psychosocial support and education is required. Unfortunately, very few intervention studies have been conducted in the last 5 years and their success is limited. Survivors of childhood cancer from the St. Jude Lifetime Cohort were enrolled in a randomized control trial for a smoking quitline.[89] Quitlines are a commonly used intervention in the general population with reports showing a 40% increase in cessation rates. All participants received free nicotine replacement products and received a cognitive behavior intervention targeted for survivors of childhood cancer. Following bioverification of smoking status at the

12-month follow-up, the success of this study was only 2%. In fact, 80% of those who reported they had successfully quit smoking at the end of the intervention were found to be using tobacco products when tested for cotinine. The high rate of falsifying smoking status may be linked to survivors of childhood cancer feeling pressure to report that they have quit smoking, especially in the context of a randomized control trial designed to assist smoking cessation.

Nagler and colleagues[105] investigated the use of health information media for informing healthy lifestyle choices in survivors of childhood cancer. Adult survivors who access health media are more likely to engage in healthy behaviors. Among a population of survivors of childhood cancer who were previously enrolled in a smoking cessation intervention, 34.2% accessed health information on television (ie, news reports) weekly, whereas 20.1% sought out information in print media and 16.7% used online sources.

Social Adjustment

Social adjustment has been broadly defined as the extent to which one attains socially desirable and developmentally appropriate goals.[106] Research overwhelmingly continues to identify survivors of childhood cancer at risk of social adjustment difficulties. Specifically, survivors of childhood cancer tend to be more withdrawn compared with their peers and are less likely to have reciprocated best friend nominations.[107] As adults, survivors are identified as at risk of having poorer outcomes including not being married, not living independently, and using social benefits compared with the general population.[108–110] Importantly, one of the most significant contributions to this literature over the last 5 years is the recommendation that opportunities for social interaction should be provided as a standard of care in pediatric oncology.[111] Although the recommendation itself is focused more on children during active cancer treatment it acknowledges that social interactions are a critical unmet need.

Evidence continues to acknowledge that survivors of central nervous system (CNS) tumors and survivors receiving CNS-directed therapies are particularly vulnerable to the development of social difficulties following cancer treatment.[112] Large cohort studies examining potential risk factors for social difficulties have revealed that radiotherapy to head and/or neck and an original CNS tumor diagnosis negatively influenced all social outcomes examined in childhood cancer survivors.[108] Using data from the Childhood Cancer survivor study, Schulte and colleagues[113] reported that survivors of CNS tumors were more likely to have 0 friends (15.3%) and to interact with friends less than once per week (41.0%) in comparison with survivors of solid tumors (2.9% and 13.6%, respectively) and siblings (2.3% and 8.7%, respectively). Desjardins and colleagues[114] reported that approximately half of survivors of pediatric brain tumors did not have any reciprocated best friend nominations and 25% were not nominated by any peer as a best friend. Social difficulties among survivors of CNS tumors may also persist into adulthood and affect relationship status.[115]

Previous reviews focused on social adjustment among survivors of cancer have highlighted the need to move away from superficial assessment of social outcomes that lack a conceptual framework for greater depth in investigation.[116] The research related to social adjustment in survivors of childhood cancer has advanced significantly in the last several years due in large part to the increased application of theoretic frameworks related to the social development in children with acquired brain injury.[117] Specifically, consideration of a theoretic framework has facilitated more comprehensive approaches to operationalizing social adjustment, which considers the need for multileveled, multiinformant assessments and also acknowledges the important role of insult-related (eg, diagnosis, treatment) and noninsult-related (eg, family functioning) risk and resilience

factors. Subsequently, the literature has gained greater specificity with respect to the components of social adjustment that might be affected as a result of cancer diagnosis and treatment, identification of those who may be at risk, and consideration of some of the potential moderating and mediating factors.

Accordingly, the last 5 years has witnessed greater homogeneity in investigation of social adjustment difficulties by diagnosis including specific considerations of retinoblastoma,[118] astrocytoma,[119] medulloblastoma,[120,121] and Wilms tumor.[88] In addition, there has been greater consideration of specific treatment effects such as hyperfractioned versus conventionally fractionated radiation therapy, revealing that long-term social outcomes were better among ALL survivors who received hyperfractioned radiation.[122]

Other factors that have been explored in the context of social outcomes include treatment-induced hearing loss, which was found to be associated with reduced social attainment.[123] In addition, more consistently, cognitive functions including attention and executive functioning are being considered in conjunction with social adjustment. Not surprisingly, there is a strong association between the 2, whereby greater cognitive dysfunction has been linked to increased social difficulties.[109,115,120,124–126]

Interventions

Over the last 5 years there has been increased attention to the development of interventions to improve social interactions with a specific focus on especially vulnerable populations, namely, survivors of pediatric brain tumor. For example, Barrera and colleagues[127] conducted a multisite randomized control trial of a group social skills intervention program designed to remediate social difficulties among survivors of CNS tumors. The results of this work revealed a statistically significant effect compared with a placebo control group for self-reported social skills that persisted after 6-month follow-up. No differences were found however, for parent-proxy or teacher reports.

Devine and colleagues[128] reported on the feasibility and preliminary outcomes of a peer-mediated intervention. The focus of this intervention was to train peer leaders to engage classmates. Although the intervention was deemed acceptable and feasible to implement in schools, no changes in peer-reported measures were noted with the exception of friendship nominations.

Most recently, consistent with efforts to improve cognitive function using computerized training and literature linking cognitive function with social outcomes, Mendoza and colleagues[129] sought to determine whether the benefits observed using computerized training generalized to social outcomes across all survivors of childhood cancer. Unfortunately results of this study did not find cognitive gains from a computerized rehabilitation program translated to an improvement in social skills.

DISCUSSION

The goal of the current review was to examine the state of the literature with respect to late effect outcomes including fatigue, pain, lifestyle after cancer treatment, and social adjustment among survivors of childhood cancer. Specifically, the authors sought to determine the prevalence of and risk factors associated with each outcome and to explore interventions that have attempted to target each outcome. With respect to each outcome examined, there is evidence to suggest survivors are at elevated risk of experiencing fatigue, pain, decreased physical activity, engagement in risky health behavior, and poor social adjustment. Risks are more pronounced for survivors of specific diagnoses or receiving specific treatment protocols (eg, survivors of CNS tumors or receiving CNS-directed therapies). However, findings remain inconclusive

as to whether prevalence is greater than or equivalent to that observed among the general population. Regardless, given survivors of childhood cancer are at significant risk for late effects of their diagnoses and treatments, there is a critical need to acknowledge these risks.

Examination of variables that may be related to the outcomes reviewed reveals critical clinical or medical risk factors including the diagnosis of a CNS tumor or treatment with CNS directed therapy.[112] Overwhelmingly, for survivors experiencing fatigue, pain, lower physical activity, engagement in risky health behaviors, or poor social adjustment, there is a strong association with poorer psychological functioning. Unfortunately, given the fact that most of the studies are observational in nature, the direction of these associations cannot be established. Longitudinal research is needed to determine the significant pathways and identify targets for intervention. Perhaps most interesting from the current review was the interrelations between the outcomes of study. Specifically, fatigue, pain, and physical activity are highly interrelated. Cognitive performance also seems to be a pervasive mediating or moderating factor. Future research should aim to study these pieces simultaneously, rather than in isolation, to gather a more comprehensive understanding of how they might be related to one another.

It was encouraging to see the implementation of interventions across the outcomes examined, with the exception of pain. However, intervention work to date has focused primarily on the management of these outcomes during active treatment. More research is needed in the management of fatigue, pain, and engagement in physical activity in the survivorship stage. For those interventions that do exist, most remain in the pilot stages of development, and more research is needed to determine efficacy. Moreover, for those that do exist, few incorporate long-term follow-up assessments, which limits the ability to draw conclusions regarding the sustained effects of the intervention on a range of outcomes. More effort is needed in the development of interventions and given the comorbidities noted earlier, interventions might benefit from multipronged targets. Once these steps have been taken, greater efforts to ensure successful implementation of interventions must be taken.

Across studies, limitations related to the existing research continue to exist. First, childhood cancer is relatively rare, and so small sample sizes are common. Published studies have typically included small sample sizes, without control groups, with participants varying in lengths of survivorship, primarily representing leukemia, lymphoma, and brain cancer survivors. This challenge is exacerbated during survivorship due to the geographic spread of survivors. Second, most outcomes reviewed (ie, fatigue, pain, physical activity, social adjustment) are complex behaviors that necessitate considering factors at varying levels (eg, individual, social, institutional). Examination of these outcomes using single-item measures are not enough. Researchers are encouraged to capture multiple dimensions of these outcomes in order to capture a deeper understanding of how survivors of childhood might be affected.

Future research in this area should focus on exploring the antecedents and consequences of these outcomes. This research would benefit from the following: including larger and more diverse groups of survivors across different cancer types and at varying stages of survivorship to ensure adequate power to detect main and subgroup effects, using/linking to existing databases and/or being multisite, including a wider range of outcomes that are important to childhood cancer survivors, consistent measures (so as to facilitate meta-analyses and enable data pooling), and longer-term interventions and follow-up. In the meantime, researchers and cancer centers should

attempt to provide high-quality and accessible health information to survivors through various media outlets to encourage healthy behaviors. Providing survivors with adequate mental health resources and appropriate education will assist them in making healthy choices.

DISCLOSURE

The authors have no conflicts of interest to declare.

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