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Review

Childhood Cancer and Treatment Effects on Motor Performance

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ABSTRACT

International Journal of Exercise Science 11(3): 657-668, 2018. Children with cancer report motor problems several years post treatment. Physical performance limitations can restrict the survivor's ability to participate fully in daily activities necessary for self-care, family life, and/or work. Motor performance in childhood cancer could be an important measure in symptom research. This review addresses motor performance limitations caused by cancer treatment in childhood cancer survivors. Several studies found performance deficits in strength and flexibility. Conflicting research in balance, coordination, and reaction time needs further consideration. The findings may indicate muscle atrophy as a cause of performance limitations rather than neurological issues caused by treatment. The evidence that suggest motor performance is affected by cancer and its treatment is still not fully understood. Larger cohorts of pediatric cancer patients during and after treatment phase are warranted to examine exercise as a preventative measure for deficiencies in motor performance.

KEY WORDS: Motor control, performance limitations, impairment, acute lymphoblastic leukemia

INTRODUCTION

Childhood cancer is the leading cause of disease-related death among 1 to 19 year olds in the United States (28). Survival rates vary across cancer type. Up to 80% of children and adolescents who are diagnosed with cancer live >5 years after cancer diagnosis (15). Cancer treatment kills cells that cultivate quickly. Healthy cells in a child are growing quickly as they are developing and growing much quicker than healthy adult cells. Treatment can damage healthy cells and keep them from developing normally. The treatment responsible for survival can produce adverse long-term health-related outcomes that can occur months or years after completion of cancer treatment. Long term health-related outcomes contribute to 60-90% of chronic health conditions developed from childhood cancer and its treatment (2, 7, 17).

Long-term impairments in intellectual, emotional, and physical functioning can be caused by malignancies and cancer treatments. Motor performance is the body's physiological response to an internal or external stimulus that causes movement. Children with cancer report motor problems several years post treatment when compared to their healthy counterparts (4, 11). Physical function and performance is becoming more relevant in symptom research (25). A number of chemotherapeutic agents used in the treatment of childhood malignancies have side effects that can lead to decreased motor performance. Children that are treated with radiation and chemotherapy are more likely to experience limitations in exercise performance than those treated with surgery alone. This is due to tissue damaging effects of the treatment (21). Performance limitations can restrict the survivor's ability to participate fully in daily activities necessary for self-care, family life, or work. Ness and Gurney (20) found the risk for performance limitations are greater in patients who had brain cancer, bone cancer, neuroblastoma, soft-tissue sarcoma, or Hodgkin lymphoma. These cancer types could be initiating neurological and/or musculoskeletal limitations in childhood cancer patients (5). Reduced levels of physical activity, physical functioning, and health related quality of life in pediatric cancer patients can cause long term impairments in physical functioning and daily activity. (3, 16, 23, 27, 33). Survivors of childhood cancer have physiological deficits inhibiting functional capacity that cannot be reconditioned by participation in regular physical activity (13).

Previous literature has suggested that motor function disability in childhood cancer patients or survivors is thought to be initiated by insufficient muscle activity leading to muscle weakness (32). This can lead to reduced physical functioning. Hoffman et al. (13) indicates that poor physical functioning in cancer patients may result from physiological deficits from treatment rather than sedentary behaviors and bed rest. In a separate study, physical performance of acute lymphoblastic leukemia (ALL) patients treated without stem cell transplant (SCT) did not differ from that of the healthy control population (26). This suggests treatment type may play a role in physiological deficits. Hypoplasia to a muscle group could be caused by both treatment and bed rest and can negatively affect the function of the musculoskeletal system. The resultant dysfunction can subsequently lead to disuse and deconditioning that can impair performance (30). This may lead to additional bed rest and therefore further weakness and further deconditioning.

The purpose of this review is to provide an evaluation of the effects of cancer treatments on physical motor performance in children diagnosed with childhood cancer. Cancer treatment can include surgical methods, chemotherapy, radiotherapy, SCT, and/or targeted therapy. Based upon current research, it is hypothesized that a decline in gross motor performance in childhood cancer patients is to be expected when compared to healthy counterparts.

METHODS

The following databases; CENTRAL, MEDLINE, PubMED, SportDISCUS, Cochrane Databases, PEDro (Physiotherapy Evidence Database), EMBASE, were used. Articles were identified by using combinations of the following key words: exercise, physical activity, physical therapy resistance, strength, cardiorespiratory, cardiovascular, training, cancer, leukemia, acute lymphoblastic leukemia, stem cell treatment, pediatric, childhood, children, adolescent, young adult, teenage. The year of publication was pre-selected in the search filter 2008-2015.

Studies were included in this review if they met several criteria. Randomized control trials, randomized clinical trials, systematic reviews, meta-analysis and cohort studies were used based on evidence strength (Level of evidence Ia-IIb; Table 1)

Table 1: Classification and judgment of the strength of evidence

Level of evidence	Type of study/publication	Strength of evidence
Ia	Meta-analysis of randomized, controlled intervention studies	Convincing[a]/Probable[b]/Possible[c]
Ib	Randomized controlled intervention studies	Probable[b]/Possible[c]
Ic	Non-randomized/non controlled intervention studies (if well designed otherwise level IV)	Probable[b]/Possible[c]
IIa	Meta-analysis of cohort studies	Convincing[a]/Probable[b]/Possible[c]
IIb	Cohort studies	Probable[b]/Possible[c]/insufficient[d]
IIIa	Meta-analysis of case-control studies	Probable[b]/Possible[c]
IIIb	Case-control studies	Possible[c]/insufficient[d]
IV	Non-analytical studies (case reports, opinions of experts, did not determine strength of evidence.	Possible[c]/insufficient[d]

[a] Is assigned if there are a considerable amount of studies including prospective observational studies and, wherever possible, randomized control studies of sufficient size, duration and quality with consistent results.
[b] Is assigned if epidemiological studies show fairly consistent relations between factor and disease, but there are noticeable weakness regarding evidence or there is evidence of an opposite relation, which does not show judgment.
[c] Is assigned if the results on an association between exposure and target disease are mainly based upon case-control studies and cross sectional studies. There are only insufficiently performed controlled intervention studies, observational studies, or non-controlled clinical trials.
[d] Is assigned if there are a few study results that indicate an association between a factor and a disease, but they are not sufficient to establish the relation. There is only limited or no evidence from randomized intervention studies

To be included, studies must have limited participation to subjects aged 18 and under at time of original diagnosis and must have been undergoing or completed cancer treatment. Participants must have started the exercise intervention within 5 years from original diagnosis.

Any test that included a form of physical activity that measured the outcome measures listed below. Location could have been at an exercise facility, or under specialists care (hospital/physical therapy center) or combination.

Primary outcome measures included: gross motor skills; coordination, reaction time, balance, strength, flexibility. Secondary outcomes are to include: physical activity level, health related quality of life. Testing was performed within 5 years of diagnosis and patients must have been currently undergoing prescriptive treatment (minimum of one treatment) or were within 3 years post cancer treatment.

After the initial search strategy, identification of studies meeting the inclusion criteria was employed. Eligible studies that met inclusion criteria within the title and abstract were obtained in full. Details for exclusion were clearly stated for the eligible studies.

Data extraction was performed using standardized forms with information regarding: the study design, participant baseline characteristics, setting, sample size, number of participants in each study, type of intervention(s), duration of intervention, randomizations and blinding procedure, type of control group, type of treatment and stage of treatment, duration of patient follow-up, outcome measures extracted will include: gross motor skills; coordination, reaction time, balance, strength, flexibility, physical activity level, health related quality of life

RESULTS

Keyword searches in CENTRAL, MEDLINE, PubMED, SportDISCUS, Cochrane Databases, and EMBASE yielded 942 studies. Duplicate studies and title search reduced initial total to 192 studies. Abstract review provided 26 studies and full article review led to 6 intervention studies between 2008 and 2014 that met the inclusion criteria (Figure 1, details of included studies are found in table 2).

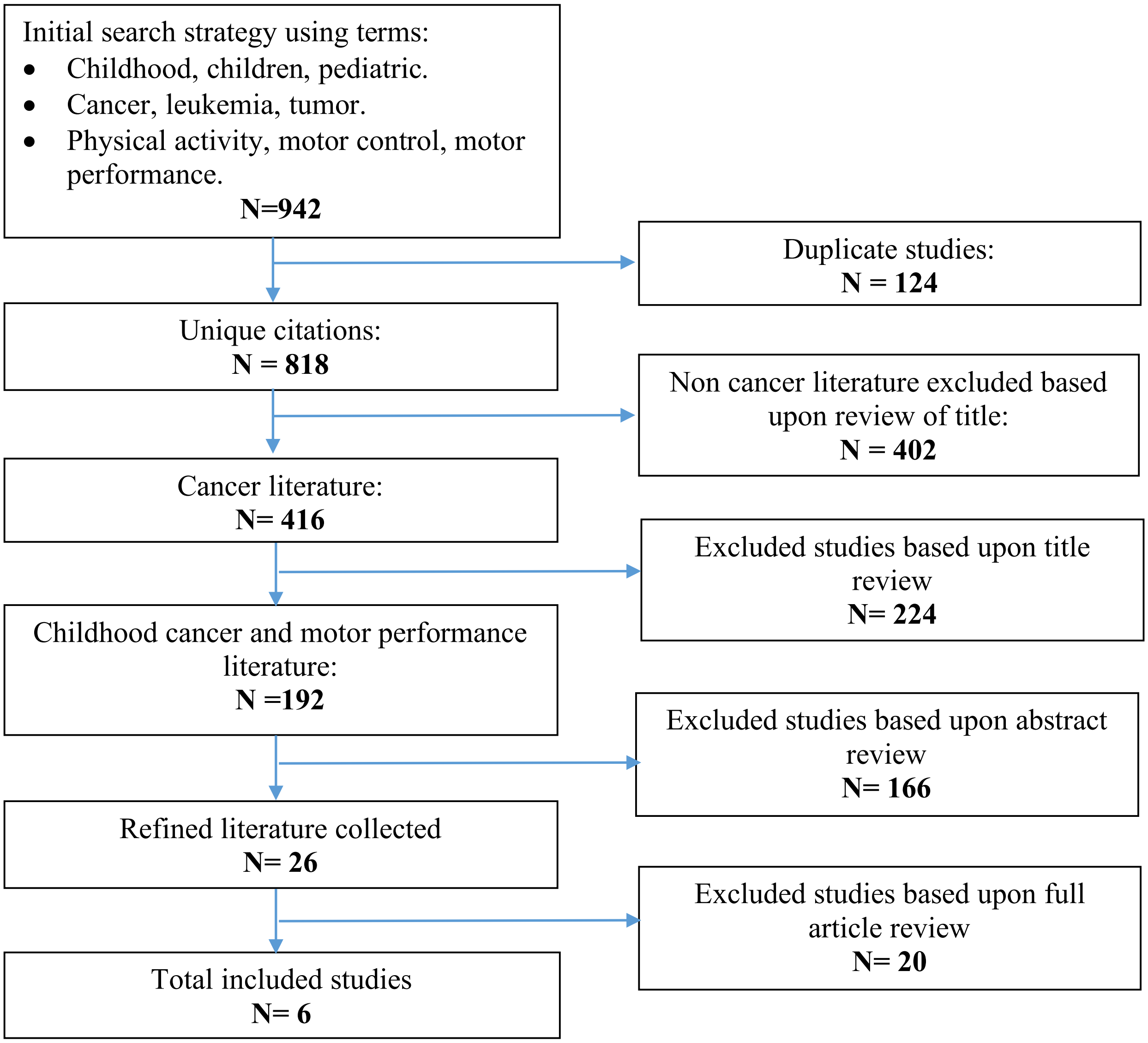

Figure 1. Search and refinement strategy for included studies.

Nineteen studies are excluded from the review for the following purposes: did not include interested age category, did not use exercise as an intervention, were qualitative in nature, used questionnaires for data collection, did not measure motor performance, and/or were review studies.

Table 2: Included studies and their characteristics

First author		Title	Type of Article	Aim	Balance	Coordination	Flexibility	Reaction time	Strength
Beulertz	2013	Specific deficit analyses in motor performance and quality of life of pediatric cancer patients-a cross-sectional pilot study	Cross sectional	Evaluate motor performance and health-related quality of life in a mixed pediatric cancer population.	✓	✓	✓	✓	✓
De Luca	2013	Gross and fine motor skills in children treated for acute lymphoblastic leukemia,	Controlled trial	Identify deficits in motor performance in young children diagnosed with ALL	✓	✓			✓
Gotte	2014	Motor performance in children and adolescents with cancer at the end of acute treatment phase	Cross sectional	Analyze motor performance at the end of the acute treatment phase and reveals potential risk factors for motor deficits	✓	✓	✓		✓
Hovi	2010	Suboptimal long term physical performance in children and young adults after pediatric allo-SCT	Controlled trial	Assess the physical fitness of transplanted children in a comprehensive manner, using a defined set of tests			✓		✓
Piscione	2014	Physical functioning in pediatric survivors of childhood posterior fossa brain tumors	Controlled trial	Describe physical functioning of pediatric survivors using a measure of physical performance validated for children	✓	✓		✓	✓
Taskinen	2014	Physical performance of no transplanted childhood ALL survivors is comparable to healthy controls	Observation	Evaluate the fitness of multiple muscle groups in a cohort of children and adolescents after modern conventional ALL therapy without SCT.			✓		✓

A total of 279 childhood cancer patients took part in the included studies. Two studies investigated the effect of treatment on motor performance in children with ALL (6, 26), 2 studies examined the effect of treatment on motor performance in children with various cancer types (4, 14), one study looked at posterior brain fossa tumors (24) and one study examined stem cell transplants and how that could affect motor performance in children (14). The ages of the children and adolescents ranged from 2.5-18.

Testing procedures and outcome measures differed between the studies. Of the 6 studies 4 measured coordination of the child (4, 6, 14, 24), 2 studies examined reaction time (4, 14), 4 considered balance (4, 6, 8, 24) all 6 measured strength of the patient (4, 6, 8, 14, 24, 26), and 4 studies examined flexibility (4, 8, 14, 26). Two studies used the same procedure and test battery (8, 26), the rest used 5 different measures (4, 6, 14, 24).

Table 3. Significant difference of outcome measures in included studies.

	Cancer	Balance	Coordination	Flexibility	Reaction time	Strength
Beulertz	All types	NS	0.01*	0.01*	NS	0.01*
De Luca	ALL	NS	NS	-	-	NS
Gotte	All types	0.01*	NS	0.01*	0.012**	0.01*
Hovi	SCT	-	-	0.01*	-	0.01*
Piscione	Brain	0.01*	0.01*	-	-	0.05**
Taskinen	ALL	-	-	0.01*	-	0.01*

NS, non-significant outcome; * p=0.01, 99th percentile; ** p=0.05, 95% percentile; - was not a measures variable

Twenty-meter sprint, push up, sit ups, and standing broad jump were used by Beulertz et al. (4) to measure strength, the child's ability to react to a stimulus to measure reaction time, sideways jumps and balancing backwards to measure balance and coordination, and forward bend to measure flexibility in 26 pediatric cancer patients, post treatment (age: 4-17). The authors found no significant difference in balance (p=1.000) and reaction time (p=0.096) when compared to reference data. Coordination (p=0.001), strength (p=0.001), flexibility (p=0.033) and the total global score (p=0.000) of the test battery were highly significant compared to the control population. There was no significant difference determined between the study group and healthy children of the same age in terms of health related quality of life (p=.380).

De Luca et al. (6) used the Movement Assessment Battery for Children-2 (MABC-2) to assess gross motor (coordination) and balance and the Bruininks-Oseretsky Test of Motor Proficiency 2nd edition short form (BOT-2 SF) to assess coordination, strength, and agility in 37 (age: 2.5-4) child survivors of ALL. 27% of children showed motor impairment in MABC-2 (balance and coordination) and 16% of children showed motor impairment in BOT-2 SF (coordination, strength, and agility).

The MOON test battery was used by Gotte et al (8) to measure motor performance of 47 pediatric cancer patients (age: 6-18). Static stand was used to test balance, an optical stimulus was used to measure reaction time, throwing at a target, measured coordination, stand and reach was used to measure flexibility, and hand-held dynamometry was used to measure strength. Balance (p=0.003), flexibility (p=<0.001), strength (p=<0.001), and reaction time (p=0.012) showed significant differences between cancer patients and reference values and coordination showed no significance (p=0.172). 55% of study participants fell below the reference value for balance, 57% for reaction time, 89% for flexibility, and 91% for strength.

Hovi et al. (14) used the leg lift test and repeated squatting test to measure strength. The sit and reach test and back extension test to measure flexibility in 94 patients who had SCT. The authors looked at early testing (1-2 years after treatment) and late testing (>4 years after treatment). The results from early testing indicated that strength and flexibility was significantly lower on all levels (p=0.001) when compared to healthy controls. Patients who had exercised more regularly and were members of a sports club (n=15) performed better in the sit and reach (p=0.002), and back extension (p=0.007).

Measurements were obtained by Piscone et al. (24) using the BOT-2 assessment for balance (9 items), coordination (7items) and strength (5items) in 30 children (age 4-18) who had previously been diagnosed with posterior fossa brain tumors, >1 year post treatment. Significant differences were found between survivors and normative data in balance (p=0.001) and coordination (p=0.001). Strength was found to be significant in the 95th percentile (p=0.026) demonstrating significantly lower gross motor functioning when compared with normative data.

Taskinen et al. (26) used the leg lift test, and repeated squatting test to measure strength and the sit and reach test and back extension test to measure flexibility in 45 ALL patients within 3 years of chemotherapy treatment. Strength testing was found to be insignificant in leg lift and repeated squatting test. Flexibility differences were significant in both the sit and reach (p=0.001) and back extension (p=0.001). BMI and physical activity level were significant factors with respect to strength tests (p=0.001) when compared to healthy controls. Patients with a BMI below median and who exercised > 3 times per week had better muscle performance.

DISCUSSION

This review evaluates motor performance limitations caused by cancer treatment in childhood cancer survivors. Findings reveal significant impairments in motor performance among children who have undergone treatment (<5 years). This is seen in strength (5 of 6 studies), and flexibility (4 of 4 studies). Cancer and its treatment may have an impact on these particular motor skills. Children who are ambulatory during and post treatment appear to be functioning normally but are severely deconditioned compared to healthy counterparts. Balance (2 of 4), coordination (2 of 4), and reaction time (1 of 2) show significant impairment when compared to norms in 50% of the studies included. The trend shows inconclusive data and more research is necessary to make an affirmative conclusion.

Taskinsen et al. (26) and De Luca et al (6) examined patients with ALL. No significant differences were found in balance (6), and coordination (6). With regards to strength, Taskinsen et al. (6) found strength to be significantly affected in ALL patients whereas De Luca et al. (6) did not find any significance. Flexibility was significantly affected in ALL patients (26). Time-off-treatment did not affect the prevalence of motor impairments on any measure (6). The study that examined SCT as a form of treatment for ALL found that normal motor functioning was impaired as SCT patients' strength and flexibility were affected (8).

Studies that did not exclude a specific cancer type (1, 4) found significant findings in pediatric cancer populations. Strength and flexibility were affected in both studies. Beulertz et al. (4) found coordination to be affected by childhood cancer yet Gotte et al. (8) did not find significant differences. Reaction time and balance were significantly different in one study (14) yet Beulertz et al. (4) found that reaction time and balance were not affected by childhood cancer and its treatment. Only one study in the review examines brain tumor patients (24). Impairments in strength, balance and coordination were observed. This was expected due to central nervous system functioning and neurological control affected by treatment to the brain.

Based upon findings, strength and flexibility are motor skills most affected by cancer and its treatment. This could be indicative of the degenerative effects of treatment and bedrest leading to atrophy and stiffness. Hoffman et al., (13) gave evidence that poor physical functioning in cancer patients may result from physiological impairments caused by treatment rather than sedentary behaviors. The muscle deficits could be neurological deficiencies caused by pharmaceutical agents. Wright et al., (32) argues that motor function disability in patients or survivors of childhood cancer is caused by insufficient muscle activity. Sedentary behavior leads to muscle weakness caused by inactivity and bed rest. Peripheral muscle strength and ankle flexibility are reduced due to bed rest and physical inactivity in children treated for cancer with chemotherapy (12) and this agrees with current findings. Muscle atrophy and altered muscle function are aggravated by sedentary habits causing catabolic effects that sedentary behavior and prolonged bed rest can induce on skeletal muscle tissue (18). Muscle atrophy and early fatigue during low-to-moderate physical tasks soon become self-perpetuating conditions. Moyer-Mileur, Ransdell, and Bruggers (19) recognized that children who are not active during treatment phase are more likely to experience side effects and a decreased overall quality of life. Muscle atrophy is a common problem in children with cancer which could be due to the catabolic effects of several chemotherapeutic agents; vincristine and/or corticosteroids (29, 31). This, along with extended physical inactivity could be contributing to reduced muscle function as seen in strength and flexibility.

Survivors of childhood cancers have an increased risk of secondary cancers, cardiovascular disease, diabetes, and other secondary diseases. It is important to provide lifestyle modifications to the survivors and their caregivers to prevent this. Interventions are needed to promote rehabilitation and maintenance of physical performance to help improve quality of life and ongoing child development. Gotte, Taraks and Boos (9) found that physical activity has a positive impact on acute side effects and late effects of childhood cancer and its treatment. The effects of exercise as a co-treatment may be used as a noninvasive, non-pharmaceutical treatment to target physical limitations post treatment. Exercise interventions are shown to improve cardiorespiratory fitness, improve muscle strength, and increase muscle mass in children following SCT. The optimal distribution of type, intensity, duration, and frequency of physical activity across a childhood cancer survivor's lifespan remains unclear. Age, gender, and site specific guidelines supports moderate physical activity levels based upon the American College Sport Medicine's (1) exercise prescription guidelines of cancer patients and general population.

The inclusion of all studies that met criteria was necessary for this review; there is a possibility that some studies may have been missed on account of human error. The comprehensive search revealed only publications in the English language and may have excluded necessary research. Only one reviewer performed the search and rated the quality of the evidence, which could have led to selection bias. A number of studies were excluded from the review because they did not exclusively meet selection criteria. Studies that were included in the review utilized small sample sizes that considered different types of cancer and treatment. The included studies used different test measures for each of the variables, with the exception of Hovi et al. (14) and Taskinen et al. (26). Some studies were the first to analyze global physical functioning in childhood cancer patients that used testing batteries that were typically developed for healthy populations.

Although the avoidance of late effects on motor performance cannot be guaranteed, the impact on participation in daily activities and physical activity can be influenced by rehabilitation strategies. The strategies are designed to restore function or prevent loss in physical performance during the treatment process. Adult survivors of childhood cancer should be monitored for functional loss throughout their lives. This is due to higher risk of performance limitations and participation restrictions they may face many years after treatment. A global test battery should be developed to test motor performance in hospital environments. Designing specific rehabilitation programs would guide further comprehensive research on the subject. Understanding which motor skills are affected by treatment allows practitioners and rehabilitation specialists to design specific programs for individuals affected by cancer treatment. This could prevent performance limitations and help improve long term effects of treatment on motor performance. Additional clinical trials regarding performance limitations are needed to examine short term and long term effects of cancer and treatment. Future studies should examine the effects of an exercise intervention on motor performance in large cohorts of pediatric cancer patients during and after treatment. This will enable researchers to identify if exercise can be used as a preventative measure for deficiencies in motor performance.

Motor performance limitations caused by cancer and its treatment in childhood cancer survivors within five years of treatment were reviewed. Strength and flexibility are the most effected motor performance variables post cancer treatment showing declines in performance when compared to healthy counterparts. This suggests that atrophy and stiffness initiated by bed rest and physical inactivity may cause deficiencies in motor performance. Conflicting research in balance, coordination, and reaction time needs further consideration. Patients with a diagnosis of cancer are at risk of becoming survivors with lasting impairments across multiple body systems. This needs to be addressed by rehabilitation professionals if these are to be appropriately identified and prevented. Health care professionals treating pediatric cancer survivors should manage physical morbidity caused by cancer and its treatment using interventions that can minimize long term impact on motor abilities. Physical activity using gross and fine motor movements should be performed by the patient as a preventative measure for secondary disease.

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