Do Childhood Cancer Survivors Meet the Diet and Physical Activity Guidelines? A Review of Guidelines and Literature

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Abstract: Despite advances in cancer treatment, childhood cancer survivors are at higher risk of developing chronic health conditions than peers who have not had cancer. Being overweight or obese adds to the already elevated risk of cardiovascular diseases and metabolic abnormalities. Diet and physical activity are modifiable behaviors that reduce obesity risk and have been shown to improve cancer survival in adult cancer survivors. Specific guidelines have been developed for cancer survivors that provide advice on nutrition, physical activity and weight management following cancer diagnosis and treatment. In this review, we report on existing nutrition and physical activity guidelines for cancer survivors, supplemented by available literature on diet and physical activity status of childhood cancer survivors and their associations with health-related outcomes. The 2012 American Cancer Society (ACS) and the 2008 Children's Oncology Group (COG) guidelines provide similar advice on diet but the ACS guidelines also offer specific advice on physical activity and weight management. Thirty-one observational studies and 18 intervention trials published prior to June 2012 that met the inclusion criteria were reviewed. Results suggest that a high proportion of childhood cancer survivors had poor adherence to dietary and physical activity guidelines. Although findings from existing intervention trials are preliminary due to small sample size, available evidence suggests that exercise intervention is safe and feasible for patients and survivors of childhood cancer. Childhood cancer survivors should be encouraged to engage in physical activity, adopt a healthy diet, and maintain a healthy weight throughout cancer survivorship.

Keywords: Childhood cancer survivors, diet, physical activity, guidelines, review.

INTRODUCTION

Advances in cancer treatment have result in increased numbers of long-term survivors of childhood cancer (i.e. cancer diagnosed before age 21 years). Childhood cancer survivors are at a much higher risk of having chronic health conditions than those who have never had cancer [1]. While it has been well recognized that being overweight or obese increases risk of cardiovascular diseases, diabetes and other chronic health conditions, childhood cancer survivors may be especially vulnerable to metabolic sequelae due to cancer treatment at a young age [2]. New evidence has emerged suggesting that maintenance of healthy lifestyle and weight improves metabolic outcomes and reduce cancer recurrence and mortality in adult cancer survivors [3]. Maintaining a healthy lifestyle may benefit childhood cancer survivors not only by preventing overweight or obesity but also by reducing risk of chronic diseases, secondary cancers, cancer recurrence and mortality.

Specific guidelines on nutrition and physical activity have been developed for cancer survivors, including those developed by the American Cancer Society (ACS) [4-6], the World Cancer Research Fund/the American Institute for Cancer Research (WCFR/AICR) [7], and the American College of Sports Medicine (ACSM) [8]. All of these guidelines focus primarily on survivors of adult cancers but contain little information for survivors of childhood, adolescent and young adult cancers. The only available guidelines specifically for childhood cancer survivors are the Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, published in 2008 by the Children's Oncology Group (COG) [9]. These guidelines do not specifically focus on nutrition and physical activity, but do include a section on "the Healthy Living after Treatment for Childhood Cancer" that provides advice on nutrition and physical activity [9]. Practitioners who care for adult patients who have survived childhood cancer might consider use of lifestyle recommendations derived from either the COG guidelines or from the ACS guidelines. While guidelines for children and adolescents need to consider growth and development, other overarching goals may be similar for both adults and children. Below we discuss the similarities and differences in recommendations found in the 2008 COG and 2012 ACS guidelines. Because the 2007 WCRF/AICR guidelines largely focus on cancer prevention and the 2010 ACSM physical activity guidelines were incorporated in the 2012 ACS guidelines, they were not included.

Since no evidence-based guidelines for diet and physical activity exist for survivors of childhood cancer,

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we also performed a literature review to assess knowledge about diet and physical activity practices and associated health outcomes in childhood cancer survivors.

I. COMPARISON OF 2012 ACS GUIDELINES AND 2008 COG GUIDELINES

Goals of the Guidelines

The ACS guidelines define a cancer survivor as anyone who has been diagnosed with cancer from the time of diagnosis through the rest of their life. As such, the ACS guidelines provide advice during active treatment and after the completion of cancer treatment. In contrast, the COG guidelines are intended for use after two or more years following completion of cancer treatment. Nevertheless, both the ACS and COG guidelines acknowledge that the nutritional needs or exercise capacities of cancer survivors may change over the course of treatment and differ across cancer type or by stage of diagnosis. Therefore, advice may need to be tailored to achieve optimal nutritional status and physical activity over the treatment continuum. The ACS guidelines recommend that nutrition assessment be conducted soon after cancer diagnosis and indicate that the overall goals during active cancer treatment should be to prevent or resolve nutrition deficiency, preserve lean body mass, and achieve or maintain a healthy weight [6]. Specific advice may be needed for patients who cannot meet their nutritional needs either due to cancer or its treatment, while after treatment the emphasis is to prevent over-nutrition and, unhealthy post-treatment weight gain.

The stated goals of the COG guidelines are to increase quality of life and decrease complication-related healthcare costs for childhood cancer survivors by providing standardized and enhanced follow-up care that promotes healthy lifestyle, provides for ongoing monitoring of health status, facilitates early identification of late effects, and provides timely intervention for late effects [9]. To ensure healthy living after cancer treatment, the COG guidelines encourage survivors to make healthy lifestyle choices. The guidelines emphasize that cancer diagnosis and its treatment should not be used as an excuse for not eating healthily and staying active physically.

Dietary Patterns Recommends by the Guidelines

Both ACS and COG guidelines emphasize cancer survivors eat a diet high in vegetables, fruits, and whole grains (Table **1**). The COG guidelines also emphasize survivors develop a plan for well-balanced diet and choose a variety of foods from all food groups. Both guidelines emphasize limiting the consumption of processed and red meats, and instead focusing more on intake of fish, poultry or beans. Both sets of guidelines advise cancer survivors to limit intake of fat, added sugar and refined carbohydrates. The COG guidelines also recommend that survivors to avoid foods with high salt content.

The ACS guidelines recommend that cancer survivors obtain needed nutrients through foods rather than supplements, while the COG guidelines offer no specific advice about supplements. Given the emerging evidence that use of some dietary supplements may have a detrimental effect on cancer survival [10], the ACS guidelines advise survivors to limit the use of supplements unless there is evidence of a nutrient deficiency and to avoid dietary supplements exceeding 100% of Daily Value unless recommended by a physician to treat other health conditions.

Regarding alcohol consumption, the COG guidelines advise cancer survivors to limit alcohol to <1 drink/day for women or <2 drinks/day for men, whereas the ACS guidelines suggest minimal alcohol consumption during active cancer treatment to prevent interference with chemotherapy or radiotherapy.

Physical Activity Recommended by the Guidelines

The ACS guidelines recommend cancer survivors follow ACSM guidelines that recommend regular physical activity, avoidance of physical inactivity, and return to normal activity soon after diagnosis or treatment [8]. Specific recommendations are found in Table **1**. In contrast, the COG guidelines do not offer specific physical activity recommendations and refer survivors to the 2006 ACS general guidelines for cancer prevention [11], as summarized in Table **1**. The difference between the updated ACS guidelines and the COG guidelines on physical activity could be due to the fact that the 2012 ACS guidelines were developed based on evidence since 2006 that demonstrates that physical activity for cancer survivors is safe, feasible, and confers substantial health benefits. These benefits include reduced cancer recurrence, improved overall mortality, improved health-related fitness outcomes (e.g., cardiopulmonary fitness, muscle strength, body composition) and various patients-oriented outcomes (e.g., quality of life, fatigue, psychosocial distress, depression) [8, 10].

Both the COG and ACS guidelines acknowledge that cancer survivors may have specific issues that

Table 1: Comparison of ACS and COG Guidelines on Nutrition and Physical Activity for Cancer Survivors

	ACS (2012)	COG (2008)
Diet *(overall)*	- Achieve a dietary pattern high in vegetables, fruits and whole grains; - Diet composition guidelines are also appropriate for cancer survivors (20-35%, 45-65% and 10-35% energy from fat, carbohydrate ad protein)	- Choose a variety of foods from all the food groups (grains, vegetables, fruits, oil, milk, meat & beans); - Use the "Steps to a Healthier You" guide to develop a well-balanced diet and activity plan (www.mypyramid.gov)
Vegetables and fruits	- Eat ≥2-3 cups of vegetables and ≥1.5-2 cups of fruits per day; consume a variety of colorful vegetables and fruits each day; - When juice is consumed, use 100% juice	- Eat ≥ 5 servings fruits and vegetables per day, including citrus fruits and dark-green and deep-yellow vegetables; - When drinking juice, choose 100% fruit or vegetable juice, and limit to 4 ounces per day
Milk/dairy	- Choose low-fat dairy products	- Choose low-fat milk and dairy products
Meat	- Limit the consumption of processed and red meats, and consume more fish and poultry	- Limit intake of red meat and substitute with fish, poultry or beans; - When eat meat, select learner or smaller portions;
Fiber	- Consume foods with good sources of fiber (beans, vegetables, whole grains, nuts and fruits)	- Eat plenty of high-fiber foods, such as whole-grain breads, rice, pasta and cereals
Fat	- Consume as few trans fats as possible; - Discourage cooking meat and other high-fat sources of protein at high temperature	- Decrease the amount of fat in meals by baking, broiling or boiling foods; - Limit fried and high-fat foods
Sugar	- Limit foods and beverages with added sugar	- Limit refined carbohydrates, including pastries, sweetened cereals, soft drinks and sugar
Salt	N/A	- Avoid salt-cured, smoked, charbroiled, and pickled foods
Alcohol	- Tailor advice to individual cancer survivor; - Avoid or keep consumption to a minimum to prevent interaction with chemotherapeutic agents, and to avoid further aggravation to treatment areas during radiation therapy	- Limit alcoholic drinks to <2 drinks per day for men and < 1 drink per day for women
Supplement	- Obtain needed nutrients through foods, as opposed to supplements; - Limit the use of supplements unless nutrient deficiency; - Avoid dietary supplements exceeding 100% of Daily Value unless recommended by a physician	N/A
Physical activity	Engage in regular physical activity - Avoid inactivity and return to normal activity as soon as possible after diagnosis or treatment; - For adults aged 18-64 years: Have moderate physical ≥ 150 minutes/week activity and/or ≥ vigorous physical activity 75 minutes/week; Have strength training ≥ 2 days/week; - For adults ≥65 years: Follow the above recommendations if possible; If chronic conditions limit activity, be physically active as their abilities allow; Avoid long periods of physical in activity. - Use behavioral support strategies	- Check with healthcare team before starting an exercise plan or taking part in new sports and recreational activities. - For adults: Engage in moderate physical activity ≥30 minutes/day for ≥5 days per week - For children and adolescents: Engage in ≥60 minutes/day of moderate to vigorous physical activity for ≥5 days per week
Weight management	Achieve and maintain a healthy weight - If overweight or obese, limit consumption of high-calorie foods and beverages and increase physical activity to promote weight loss	Consult with health care team and a nutritionist to develop a nutrition plan for weight loss.

affect their ability to exercise and that specific cautions may be indicated. The COG guidelines suggest that cancer survivors consult their physicians before starting an exercise plan or engaging in new types of physical

activities, and encourage survivors to initiate an exercise regimen slowly and provide advice to avoid injuries. The ACS guidelines advise survivors with comorbidities to modify their exercise program in consultation with physicians. For example, the ACS guidelines suggest that survivors who are experiencing severe fatigue might consider 10 minutes of light exercise daily.

Weight Management Recommended by the Guidelines

The COG guidelines advise survivors to consult with physicians and nutritionists to develop a plan if the survivor needs to lose weight but do not provide specific recommendations. The ACS guidelines, however, clearly advise cancer survivors, regardless of weight status at diagnosis, to achieve and maintain a healthy weight, as defined by a body mass index (BMI) 18.5-25 kg/m^2. For survivors who are at risk of unintentional weight loss due to cancer itself or its treatment, the advice is to maintain positive energy balance and increase weight. However, because many patients are overweight or obese at the time of the cancer diagnosis and there is increasing evidence showing that being overweight or obese increases the risk of cancer recurrence and reduces survival [10], ACS advice for overweight or obese survivors, even during treatment, is to limit consumption of high calorie foods, increase consumption of vegetables, and increase physical activity to promote weight loss. The ACS guidelines further suggest that modest weight loss (≤ 2 pounds/week), when closely monitored during treatment, is not contraindicated with cancer treatment. After cancer treatment, intentional weight loss, managed with a combination of dietary, physical activity and behavioral strategies, even when modest (e.g. 5-10%), confers significant health benefits for cancer survivors.

Summary of Current Guidelines

Overall, nutrition and physical activity guidelines for cancer survivors do not differ substantially from the general diet and physical activity guidelines developed by federal agencies, such as the Dietary Guidelines for Americans (DGA) [12] and the Physical Activity Guidelines for Americans [13, 14]. It is interesting to note that, while cancer survivors appear to be at increased risk for excess body weight and for weight-related morbidity compared to the general population, current guidelines for survivors are in general no more stringent than the DGA, which are directed at the healthy population at large. In fact, the dietary guidelines for cancer survivors are more general than the DGA and do not offer specific strategies for implementation, which likely reflects the relatively smaller body of evidence supporting specific recommendations for survivors. The ACS guidelines provide advice in areas of nutrition, physical activity and weight management for all cancer survivors from diagnosis through survivorship. Although the COG guidelines provide nutrition and physical activity advice specifically for childhood cancer survivors, the guidelines have not been updated since 2008 and thus may not reflect more recent evidence regarding how diet, physical activity and weight management may affect the long-term health in childhood cancer survivors. To address that gap, we embarked on a systematic review of the literature, summarized below.

II. EVIDENCE FOR DIET AND PHYSICAL ACTIVITY ASSOCIATIONS WITH HEALTH OUTCOMES IN CHILDHOOD CANCER SURVIVORS

Search Strategy

We searched PubMed for observational studies and interventional trials published prior to June 2012 that assessed diet and physical activity in childhood cancer survivors and associated health outcomes, using the medical subject heading (MeSH) and text words “childhood cancer survivors” or “pediatric cancer survivors” in combination with “diet”, “nutrition”, “physical activity”, “exercise” or “lifestyle”.

Studies were included in this review if they met the following criteria: (1) were research articles published in peer-reviewed journals; (2) included patients diagnosed with cancer prior to age 21 years; (3) addressed diet and/or physical activity or their associations with health-related outcomes; and (4) English language abstract available.

The search identified 173 studies that included one or more of the MeSH headings or text words. An initial review of the titles and abstracts yielded 72 papers that appeared to meet the above inclusion criteria. Full texts of the 72 papers were obtained and reviewed, a process that eventually identified 49 studies that met the inclusion criteria, including 31 observational studies and 18 intervention trials. Data from the final 49 studies were abstracted in five categories: authors and published year; study design and characteristics of the study population; exposure measured (for observational studies) or intervention components (for intervention trials); outcome measured; and primary

findings. We performed separate reviews for observational studies and intervention trials.

RESULTS

Published studies that addressed diet and physical activity in childhood cancer patients or survivors and associated health outcomes were mostly conducted among child, adolescent and young patients or survivors less than 30 years old. Non-Hispanic whites were the dominant study population whereas minority groups were not frequently included as the study population. Approximately half of the studies were conducted among survivors of acute lymphoblastic leukemia (ALL).

Observational Studies

Diet

There were 14 observational studies that evaluated dietary intake in childhood cancer patients/survivors [15-28]. However, few studies examined survivors' dietary intake in association with health-related outcomes.

Dietary Patterns and Nutrient Intake in Childhood Cancer Survivors

Dietary quality was evaluated using the Healthy Eating Index (HEI) [27] or adherence to the AICR guidelines for cancer prevention and general federal guidelines such as DGA [24]. The results suggested a poor adherence of childhood cancer survivors to these dietary guidelines. Overall, childhood cancer survivors had a low percentage of eating ≥5 servings per day of vegetables and fruits [18, 23, 24], and consumed fewer whole grains [27] but had a higher percentage of elevated energy from fat [18, 24, 27] and refined carbohydrates [27] than recommended by the dietary guidelines. One study also reported that childhood cancer survivors consumed 10% higher total energy than estimated energy expenditure, based on survivor's age, gender, weight, height and levels of physical activity [17].

For calcium and vitamin D intake, three studies demonstrated a high percentage of childhood cancer survivors did not meet the Recommended Dietary Allowance (RDA) for calcium [18, 27] or vitamin D [27], or the Estimated Average Requirement (EAR) (32%) for calcium intake [17]. However, one study that examined serum vitamin 25(OH)D levels in 95 long-term survivors of hematopoietic cell transplant (HCT) found that the majority (64%) of survivors of HCT had sufficient vitamin D concentrations [28]. Because 61% of the HCT survivors also reported regular use of vitamin D supplements, this result is likely to reflect the vitamin D supplemental use in HCT survivors in the study's sample. A high percentage of childhood cancer survivors were also found not to meet the EAR for folate and iron (50% and 44% respectively) [17], or RDA for folate (48%), potassium and magnesium (>70%) [27].

Diet has been assessed using different methods in childhood cancer survivors. Two studies used food frequency questionnaire (FFQ) [24, 27], one study used 3-day food diary (2 weekdays and 1 weekend) [17], and one study used two 24-hour diet recalls [19] to measure dietary intake. In many studies, food/nutrient screening questionnaires or a single item question assessing fruits and vegetables intake was used. Therefore, the existing evidence for the absolute intake of food groups and nutrients from these self-reported assessments need to be interpreted with caution due to inherent inaccuracy as well as potential biases from under- or over-reporting. Only one study used biomarkers (i.e., serum vitamin 25(OH)D) in conjunction with self-reported dietary data. None of the published studies included a control group. Five of the 13 studies had a sample size below 50 [20, 22, 23, 25, 26]. All published studies used a cross-sectional design.

Dietary Intake and Health Outcomes

One study reported a moderate correlation between dietary fat intake and survivors' weight status ($r = 0.3$-0.6, $P<0.0001$) [15]. Another study reported no association between caloric intake and prevalence of obesity [20]. Bias in reporting accuracy plagues studies in this area. One study found a high percentage of childhood cancer survivors underreporting total energy intake (39%), in particular among survivors who were overweight (64%) [19]. After excluding survivors with under-reporting, weight status was not associated with total energy intake. One study examined milk and dairy products consumption with bone mineral density (BMD) in 28 survivors of childhood ALL but found no associations [25].

In summary, prospective evidence is needed that overcomes the methodological limitations such as recall bias when studying nutrition in childhood cancer survivors. Not surprisingly, overweight survivors tend to under-report intake as do overweight non-survivors but the degree to which under-reporting in these groups is similar or different is unknown. The quality of future

observational studies would be improved by use of a validated dietary assessment method or objective biomarkers, inclusion of a comparison group and sufficient sample size.

Physical Activity

There were 25 observational studies that evaluated physical activity in childhood cancer survivors [15, 16, 18, 20-22, 25, 26, 29-45], however, none of the studies examined physical activity in association with recurrence or survival outcomes.

Physical Activity in Childhood Cancer Survivors

Eight studies that assessed physical activity level in childhood cancer survivors came from Childhood Cancer Survivor Study (CCSS) [16, 29, 30, 32, 33, 37, 38, 44]. CCSS assessed physical activity using six questions from the Behavior Risk Factor Surveillance System (BRFSS) that allows one to evaluate whether subjects meet the CDC guideline for physical activity as well as if subjects engaged in any leisure-time physical activity in the past month [13]. Among the two CCSS studies that included a control group [32, 38], survivors were found to be 20-40% more likely not to meet the CDC guidelines, and 60-70% more likely to be physically inactive, when compared to sibling controls [38] or healthy controls [32]. Overall, various reports from CCSS found approximately 50-70% of survivors of childhood cancer did not meet the CDC guidelines for physically activity, although definitions of meeting physical activity varied across studies.

Other studies have demonstrated patterns of reduced physical activity in survivors similar to the CCSS studies, including use of the 2009 BRFSS survey comparing 651 childhood cancer survivors to 142,932 non-cancer peers (73.3% vs. 77.9%, OR=0.7, 95%CI: 0.6-0.9) [40], and another population-based study assessing survivors of all cancer types from the 2003-2006 National Health and Nutrition Examination Survey (NHANES) [46]. This study using accelerometers to assess physical activity actually revealed very low percentages of both cancer survivors and the general population meeting the CDC guidelines (4.5% and 12.7% respectively) but consistent with other studies the cancer survivors were more likely to fail to meet CDC guidelines (OR=1.7, 95%CI: 1.0-2.9).

Compared to CCSS and BRFSS surveys that included childhood cancer survivors with a mean age of 30 years or older, other studies assessed levels of physical activity in adolescent (11-18 years) and younger adult survivors (19-25 years) of childhood cancer [15, 18, 20-22, 25, 26, 31, 35, 36, 39, 41, 43, 45]. Physical activity assessment methods varied across these studies with some using the Godin Leisure-Time Exercise Questionnaire (GLTEQ) that quantifies the amount and intensity of exercises in a typical 7-day period [15, 18, 25, 34-36, 39], two using the Youth Risk Behavior Surveillance Survey (YRBSS) that assesses the number of days in the past week with moderate to vigorous physically activity [15, 43]. Other studies employed a variety of methods to quantify activity over periods up to one year participation in sports activities [18, 22, 26, 31, 41, 45]. Despite these methodological differences, these studies found that 50-80% of the adolescent or young adult survivors of childhood cancer did not adhere to CDC guidelines for physical activity [15, 18, 22, 26, 43, 45], which is similar to estimates in older adult survivors of childhood cancer.

Five studies comparing levels of physical activity in childhood cancer survivors to controls. However, no clear pattern was identified. Three studies suggested that young adult survivors were significantly less active than healthy controls [20, 25, 34] whereas the other two studies reported either higher levels of physical activity in survivors than in controls [42] or no difference [41]. Two studies from the same authors assessed physical activity levels prior to diagnosis, during treatment, and after treatment in adolescent and young survivors of childhood cancer [35, 36]. Their findings revealed a significant decline of physical activity as defined by <27 metabolic equivalents/week, during cancer treatment compared to pre-diagnosis (26.4 vs. 84.5% “being inactive”), a phenomenon which persisted for most after completion of treatment (73.6% “being inactive”) [36].

Physical Activity and Health Outcomes

Among the few studies that assessed other health-related outcomes in childhood cancer survivors, one large cross-sectional study from the Childhood Cancer Survivor Study (CCSS) (N=9,284) reported a 10% increased risk of becoming obese in association with low levels of vigorous physical activity (less than 30 minutes per day of vigorous physical activity for at least three days a week) [33].

Two studies assessed physical activity in association with bone mineral density (BMD). One study found that low activity levels, as assessed by accelerometers, were associated with low lumbar BMD in 28 survivors of ALL [25]. Another study, conducted in 319 survivors of childhood cancer, found lower physical

activity and higher sedentary behavior was each significantly associated with having a low BMD z-score ≤ -1 [41].

Two studies assessed psychosocial outcomes with physical activity [35, 39]. One study that assessed health-related quality of life (HRQOL) found a modest association between leisure-time physical activity and HRQOL [39]. The other study assessed current psychosocial well-being and found that physical activity was associated with improved general self-concept and four self-concept subscales (physical abilities, opposite sex relations, same sex relations and parental relations) [35].

Summary of Observational Studies

Most, but not all, studies reported reduced levels of physical activity in survivors. Nevertheless, similar to studies assessing diet, few studies examined physical activity with health-related outcomes. Objective measures using accelerometers for example, have not been employed except for the NHANES study that included survivors of all cancers. Most of these studies assessed physical activity at one-time point and few studies were prospective.

Intervention Trials

Of the18 intervention trials conducted among childhood cancer patients or survivors focusing on nutrition or physical activity, four were published in the last two years, and 11 were published between 2006 and 2010. Nearly all trials were exercise interventions, and only two trials incorporated a nutritional component that consisted of printed educational material sent to participants and/or nutrition review or counseling by a dietitian [47, 48]. Various experimental designs were used. Six (33.3%) were randomized controlled trials (RCT) [47-52], one was a cross-over randomized trial [53], five (27.7%) were non-randomized controlled trials [54-58], and six (33.3%) involved survivors or patients only for pre- and post-intervention comparisons [59-64]. Ten (55.6%) of 18 intervention trials were conducted among childhood cancer patients who were still receiving treatment (i.e., on-treatment) [48-50, 52, 53, 55, 56, 58, 59, 62], and eight (44.4%) trials focused on survivors who have completed cancer treatment (i.e., off-treatment) [47, 51, 54, 57, 60, 61, 63, 64]. Half of the trials were conducted among ALL patients or survivors, and others recruited survivors or patients with a variety of cancer diagnoses, among which two included pediatric cancer patients who received stem cell transplant [55, 57].

The published intervention trials have various intervention components, frequencies, durations and modes of delivery. Half of the interventions were delivered in the clinics or hospitals where patients or survivors receive regular care [49, 50, 52, 53, 55-57, 62, 63]. These interventions were often supervised by physical therapists [49, 52], exercise trainers [53, 55, 57, 62] or study team members [50]. Some interventions were home-based or involved a component of home-based exercise program [47, 48, 51, 54, 58-60], and others were conducted in an academic institution [61] other than the treating facility, or in community-based physiotherapy centers [64]. Nearly all programs included aerobic exercise, although only a few studies described the goals for its intensity, which ranged from 40 to 85% of maximum heart rate (HR_{max}) in published trials [55-58, 62, 64]. Over half of the trials consisted of both aerobic exercise and strength or flexibility programs [49, 52, 55, 57, 59, 61, 62, 64]. Exercise duration was typically 30-45 minutes for aerobic exercise intervention, and 45-60 minutes interventions of combined aerobic and strength training. The frequency of the exercise program ranged between twice daily (2x/d) and two days per week (2x/wk), and the study duration varied from six weeks to two years. Some trials followed subjects post-intervention to assess whether the desired outcomes could be retained after active exercise programs stopped [51, 61, 62]. Despite these differences in exercise treatment, a common theme of all intervention trials is that the exercise programs were individualized, based on survivors' capacity to exercise, and focused on a progressive increase in intensity and or duration.

Various health-related outcomes were assessed in these intervention trials. Physical outcomes included aerobic capacity or cardio-pulmonary fitness, muscle strength, flexibility, and functional mobility. Some evaluated anthropometric outcomes, such as body mass index and body composition, or diet and levels of physical activity as the outcome. For psychological outcomes, HRQOL and fatigue were the most commonly measured ones.

Aerobic Capacity

Three studies reported significant improvements in peak oxygen consumption (VO_{2peak}), either by pre- and post-comparison [60, 62] or compared to healthy controls [57], whereas two other studies assessing VO_{2peak} before and after exercise intervention found no changes [63, 64]. Three studies that assessed cardio-pulmonary function using a 20-mile shuttle run test (i.e.,

the Progressive Aerobic Cardiovascular Endurance Run) [48] or 1-mile [61] or 9-minute [52] run-walk tests reported no impacts from the exercise intervention, when comparing results pre- and post-intervention [48, 61] or comparing to randomized controlled groups [52].

Muscle Strength

One study used a dynamometer to measure maximum muscle strength for six muscle groups (shoulder abductors, keen extensors, foot dorsal flexors, hip flexors and grip strengths) and reported no impact following exercise intervention [65] whereas two studies also using a hand-held dynamometer showed significant improvements in knee extension strength in the intervention group compared to the randomized controls [52]. Another RCT used push-ups to measure muscle strength and endurance and showed no difference between the intervention and control groups [48] whereas another pre- and post comparison study measuring push-ups showed significant improvements in the upper-body strength following intervention [61]. Two studies from the same investigators measured muscle strength using seated bench press, seated lateral row and seated leg press, one involving pre- and post- comparison, the other involving nonrandomized controls, with both reporting significant improvements in muscle strength associated with exercise interventions [57, 62]. One study measured various aspects of muscle strength following exercise intervention and the results were mixed [60].

Functional Mobility

Four studies evaluated functional mobility using the Timed Up and Go test (TUG) or the Timed Up and Down Stairs test (TUDs). Two of these studies (1 RCT and 1 pre-and post-comparison) showed no effect [52, 65] and the other two studies (1 nonrandomized controlled trial and 1 pre-and post-comparison) reported significant improvements following intervention [57, 62]. One RCT evaluated motor performance using a test battery (i.e., Movement Assessment Battery for Children) and reported no effect of exercise on motor performance [49] whereas another study found significant improvement in gross motor performance following exercise intervention using the Gross Motor Function Measure [59].

Anthropometry

Four studies measuring BMI consistently reported no impact of exercise intervention on BMI [48, 49, 55, 65]. Five studies assessed body composition and none reported that exercise intervention influenced body fat or fat-free mass [48, 49, 55, 65, 66].

Bone Mineral Density (BMD)

One RCT assessed BMD following exercise intervention and reported no effect of exercise on BMD [49].

Diet

One RCT provided a nutritional intervention consisting of printed educational material and nutrition review revealed no significant effect on intake of energy, macronutrients or micronutrients [48]. Another RCT aiming to improve bone health behavior through nutrition counseling and health education found significant increase in self-reported milk consumption, and supplemental and dietary intake of calcium [67]. The other RCT that aimed to set health goals and commitment goals for survivors to practice healthy behaviors found a significant reduction in junk food consumption reported by the survivors following the intervention [51, 66].

Physical Activity

Two studies evaluated levels of physical activity following exercise intervention using questionnaires or 3-day physical activity records [48, 61]. Although both reported improvements in physical activity, neither reached statistical significance at the end of the intervention. In addition, the improvements in levels of physical activity were not able to be maintained at 3-month and 12-month post intervention [61].

Immune Function

Two studies measured completed blood counts, counts of different lymphocyte subpopulations (lymphocytes T, NK, NKT, CD4+, CD8+ and dendritic cells) and neutrophil function [55, 56] following exercise intervention. The findings indicated similar blood counts, neutrophil counts and neutrophil responses between the intervention and non-randomized controlled groups.

Health-Related Quality of Life (HRQOL)

Six studies assessed HRQOL using the Pediatric Qualify of Life Inventory (PedsQL) [52, 59, 61], the Child Health Questionnaire (CHQ) [53], or the Child's Health and Illness Profile-Child Edition (CHIP-CE/CRF) [57, 62]. Four studies reported significant improvements in HRQOL [53, 57, 59, 61] following exercise intervention, whereas the other two studies reported no effects [52, 62].

Table 2: Intervention Trials on Diet and Physical Activity in Childhood Cancer Survivors

Authors	Study population & design	Intervention Component	Outcome Measures	Major findings
Jarvela *et al* 2012 (60), Finland	Survivors of ALL (N=17) Mean age = 23.0 (16-30) yr Off-treatment (>10 yrs after diagnosis) Pre- and post-intervention comparison	Home-based program that consists of muscle strength training (3-4x/wk) and aerobic exercise (~30 min per session, ≥3x/wk) for 16 weeks; Subjects were contacted by phone at 2x/wk for counseling and motivation	- Aerobic capacity ($VO_{2peak,}$ maximum work load) - Muscle strength - BMI, % fat (skinfold thickness),WC, WHR - Physical activity (questionnaire) - Blood pressure - lipids, insulin, glucose	- Improvement in VO_{2peak}, maximum work load and muscle strength; - Decrease in WC, WHR and % fat but no effect on BMI; - Decrease in SBP, insulin and HOMA-IR but no effect on glucose and lipids; - No effect on reported physical activity - Recruitment rate = 22%
Gohar *et al* 2011 (59), US	Patients of ALL (N=9) Median age= 4 (2-14) yr On-treatment (within 2 wks after diagnosis) Pre- and post-intervention comparison	Home-based program that consists of stretching (5d/wk), strengthening (5d/wk), and aerobics exercise (10-30min per session, 5d/wk), for approximately 6-7m1onths	- Gross motor function (GMFM) - Health-related quality of life (PedsQL) - Parent satisfaction	- Improvement for gross motor function; - Overall improvement in QOL although decline observed at DI phase; - 100% parent satisfaction
Yeh *et al* 2011(58), China	Patients of ALL (N=24) Mean age = 11-12.5 yr On-treatment (receiving maintenance therapy) Non-randomized controlled trial (intervention N=14; control N=10)	Home-based program that consists of aerobic exercise (~30 minutes per session, 3x/wk), for 6 weeks; Goals: 5 min warm-up + 5 min cool-down (10-30% Heart Rate Reserve); 25-min aerobic exercise (40-60% Heart Rate Reserve)	- Fatigue (PedsQL-MFS) - Perceived exertion (Children's OMNI-walk/run scale) - Stage of chance for exercise behavior	- Moderate improvement in general fatigue at 1 month after intervention (P=0.06) but no effect on three fatigue subscales; - Recruitment rate = 80% - Drop-out rate = 14% - Adherence rate = 67-83%
Mays D 2011 (67), US	Survivors of childhood cancer (N=75) Mean age = 14.2 yr Off-treatment (≥1 year off-treatment) Randomized controlled trial (intervention N=38; control N=37)	A half-day behavioral group session on nutrition (i.e., calcium consumption) and bone health behaviors, followed by up to 3 booster phone calls over a one-month period	- Milk consumption - Calcium supplement and dietary calcium intake	- Significant increase in self-reported milk consumption, use of calcium supplement and dietary calcium intake - Recruitment rate = 49%
Speyer *et al* 2010 (53), France	Patients of childhood cancer (N=30) Mean age= 13.6 (2.9) yr On-treatment (during hospital stay) Cross-over randomized trial	Clinic-based program that consists of gamed-based physical activity (30min per session, 3x/wk during each hospital stay), for 4 hospital stays	- Health-related quality of life (CHQ)	- Significant improved HRQOL - Recruitment rate=79.5%
Chamorro-Vina *et al* 2010 (55), Spain	Patients of hematopoietic stem cell transplant (N=20) Mean age = 7-8 yr On-treatment (during hospital stay) Non-randomized controlled trial (intervention N=7; control N=13)	Clinic-based program that consists of resistance (2x/wk at 1 set of 12-15 repetitions per exercise) and aerobic exercise training (3x/wk at 50-70% HRmax), 25-30 min per session, for 3 wks	- Immune function (CBC, lymphocytes subpopulation) - BMI, FFM (skinfold thickness) - Resting HR - muscle strength	- Significant decrease in resting HR and increase in strength for the intervention group; - No effect on BMI, FFM and immune function; - Recruitment rate = 64%; - Adherence rate = 90%
Hartman *et al* 2009 (49), The Netherlands	Patients of ALL (N=51) Median age = 5.4 yr On-treatment Randomized controlled trial (Intervention N=25; Control (N=26)	Clinic-based program that consists of exercise to maintain hand and leg function (1x/d), and stretching/jumping exercise to prevent reduction in BMD (2x/d), follow-up sessions every 6 weeks, for 2 years	- BMI, body composition (DEXA) - BMD - Motor performance (BSID-II) - Flexibility (passive ankle dorsiflexion)	- No effect on BMI, % fat, BMD, motor performance, passive ankle dorsiflexion; - Recruitment rate=67%; - Adherence rate=11%

(Table 2). Continued.

Authors	Study population & design	Intervention Component	Outcome Measures	Major findings
Moyer-Mileur *et al* 2009 (48), US	Patients of ALL (N=13) Mean age=5.9-7.2 yr (4-10) On-treatment (starting maintenance therapy) Randomized controlled trial (Intervention N=6; control N=7)	Home-based program that consists of exercise and nutrition intervention; Exercise Intervention includes mod-vigorous activity, 15-20min per session, 3×/wk, for 12 months; Nutrition intervention includes printed educational material and nutrition review by a dietitian; Physical activity and nutrition intake recorded by parents	- Physical activity (activity records and pedometer steps) - Aerobic capacity (PACER test) - Muscle strength and endurance (push-ups) - Flexibility (FFF test) - Dietary intake (records) - BMI, % fat (BIA)	- Improved regular physical activity and aerobic capacity; - No effect on strength and flexibility; - No effect on dietary intake; - No effect on BMI, % fat
Takken *et al* 2009 (65), The Netherlands	Survivors of ALL (N=9) Mean age= 9.3 ± 3.2 yr Off-treatment (≥6 months after completion of chemotherapy) Pre- and post-intervention comparison	Community-based program (at a local physiotherapy practice) that consists of resistance and aerobic exercise (66-90%HR_{max}), 45 min per session, 2×/wk, for 12 wks; Plus home-based program that consists of five basic exercises for enhancing strength, flexibility and aerobic fitness, 2x/wk, for 12 wks	- Feasibility; - BMI, % fat (skinfold thickness); - Muscle strength (dynamometer); - Functional mobility (TUG, TUDS); - Cardio-pulmonary function (CPET) ; - Fatigue (CIS-20)	- No effect on BMI and % fat; - No effect on muscle strength, functional mobility and cardio-pulmonary fitness; - No effect on fatigue; - Recruitment rate = 56%; -Drop-out =44%
San Juan *et al* 2008 (57), Spain	Survivors of childhood leukemia who underwent bone marrow transplant (N=8) Mean age= 10.9± 2.8 yr Off-treatment (≤12 months after BMT) Non-randomized controlled trial (intervention N=8, healthy control N=8)	Clinic-based program that consists of resistance (1 set of 8-15 repetitions) and aerobic exercise (50-70%HRmax), 90-120min per session, 3x/wk, for 8 wks	- Aerobic capacity (VO_{2peak}); - Muscle strength, flexibility; - Functional mobility (TUG 3m, TUG 10m, TUDS) - Health-related quality of life (CHIP-CE/CRF)	- Improvement in muscle functional capacity, VO_{2peak}, muscle strength, and HRQOL; - No effect on BMI, flexibility
Keats *et al* 2008 (61), Canada	Survivors of childhood cancer (N=10) Mean age= 16.2± 1.6 yr Off-treatment (62.5 months post diagnosis) Pre- and post-intervention comparison	Institutional-based program (at an academic institution) that consists of education (30 min), and aerobic (45 min) and strength & flexibility training (15min), 1x/wk, for 16 wks Followed at 3-monht and 1-year post intervention	- Feasibility - HRQOL (PedsQL) - Fatigue (PedsQL-MFS) - Physical activity (GLTEQ) - Physical fitness (Fitnessgram)	- Increased strength, flexibility, PA, and improved HRQOL; - Decreased fatigue; - Adherence rate =81.5%; - Long-term adherence at 3-month and 1-year was low
Blaauwbroek *et al* 2008 (54), The Netherlands	Survivors of childhood cancer (N=46) Mean age = 29.8± 8.6 yr Off-treatment Non-randomized controlled trial (intervention N=46, sibling control N=36)	Exercise counseling (motivational interviews) through initial home visit followed by phone (wk3, wk6 and wk9), for 10wks Subjects were followed at the end of intervention and 9-month after intervention	- Fatigue (CIS)	- Significant decrease in fatigue in intervention group; no improvement in fatigue in controls; - Recruitment rate = 9.6% - Drop-out rate =17.4%
San Juan *et al* 2007 & Ruiz *et al* 2010 (62, 69), Spain	Patients of ALL (N=7) Mean age= 5.1 (1.2) yr On-treatment (receiving maintenance therapy) Pre- and post-intervention comparison	Clinic-based program that consists of resistance (one set of 8-15 repetitions of 11 exercise) and aerobic training (30 minutes at >70% HRmax), 3x/wk, for 16 weeks Followed by 20 weeks of detraining with no structured exercise program	- Aerobic capacity (VO_{2peak}) - Muscle strength - Functional mobility (TUG 3m, TUG 10m, TUDS) - HRQOL (CHIP-CE/CRF) - IGF, IGFBP and GH	- Significant improvement in physical fitness, strength and functional mobility at the end of intervention; - Strength and functional mobility maintained; physical fitness partially maintained - No effect on HRQOL - No effect on IGF, IGBP and GH - Adherence rate = 85%

(Table 2). Continued.

Authors	Study population & design	Intervention Component	Outcome Measures	Major findings
Hinds *et al* 2007 (50), US	Patients of childhood cancer (N=29) Mean age = 11.9 or 13 yr On-treatment (starting chemotherapy) Randomized controlled trial (Intervention N=14; control N=15)	Clinic-based program that consists of pedaling a stationary bicycle-style exercise for 30 min, 2×/day, for 2-4 days during hospital stay, for a total of 29 months	- Fatigue (FS-C, FS-A, FS-P, FS-S) - Sleep duration and efficiency	- No effect on sleep duration, efficiency and fatigue - Adherence rate = 85.4%
Ladha *et al* 2006 (56), Canada	Patients of ALL (N=4) Mean age= 11.3 ± 5.3 yr On-treatment (receiving maintenance therapy) Non-randomized controlled trial (Intervention N=4, healthy controls N=6)	Clinic-based program that consists of 30 min bouts of moderate to vigorous exercise (intermittent run-walk on a treadmill, 70-85% HRmax) , 2×/wk, for 12 wks	- Immune function (CBC, neutrophil count & function)	- Similar effects of exercise on neutrophil count or immune function between intervention group and healthy controls; - Recruitment rate=40%
Marchese *et al* 2004 (52), US	Patients of ALL (N=28) Mean age = 7.7 (4-15) yr On-treatment (receiving maintenance therapy) Randomized controlled trial (intervention N=13; control N=15)	Clinic-based program that consists of stretch, strength and aerobic exercise, 20-60 min per session, for a total of 5 sessions across 12 wks; Plus home-based sessions that consists of stretching (5d/wk), strengthening (3d/wk) and aerobic exercise (daily), for 4 months	- Muscle strength and flexibility - Functional mobility (TUDS) - Cardiovascular endurance (9 min run-walk test) -Health-related quality of life (PedsQL)	- Improved muscle strength & flexibility; - No effect on cardiopulmonary endurance , functional mobility or HRQOL; - Recruitment rate = 85% - Drop-out rate= 8%
Hudson *et al* 2002 & Cox *et al* 2005 (51, 66), US	Survivors of childhood cancer (N=272); Mean age = 15 yr; Off-treatment (~10 years from diagnosis); Randomized controlled trial (intervention N=136; controls N=136)	Multiple-behavior Intervention that consists of (1) distribution and discussion of a written "After Completion of Therapy Clinical Summary"; (2) health behavior training of setting health goals; (3) health goal commitment to practice chosen behavior; and (4) follow-up phone calls at 3-month and 6-month to reinforce behavior training	- Health knowledge - Health motivation - Health practices (smoking, sun protection, diet, exercise, etc)	- Improvement in health knowledge (perceptions about the need to change behavior, and the effort needed to stay healthy) and some health practices (breast/testicular self-examination), and decease in some risk behaviors (junk food consumption); - Gender difference were found; - Recruitment rate = 86%; - Drop-out rate= 2%
Sharkey *et al* 1993 (68), US	Survivors of childhood cancer (N=10) Mean age= 19± 3 yr Off-treatment (≥1 year off treatment) Pre- and post-intervention comparison	Clinic-based rehabilitation program consists of aerobic exercise, 30-45 min per session, 2×/wk, for 12 wks Combined with home-based program that consists of aerobic exercise, 30-45 min per session, 1x/wk, starting wk7, for 6 wks	-% fat (skinfold thickness) - Aerobic capacity (VO_{2peak}, heart rate $_{peak}$, cardiac index $_{peak}$, stroke volume index $_{peak}$, anaerobic threshold, total exercise time)	- No effect on % fat; - No effect on aerobic capacity except for significant increase in exercise time; - Drop-out rate=16.7%

Fatigue

Five studies assessed fatigue following exercise intervention: two used the PedsQL Multidimensional Fatigue Scale (MFS) [58, 61], two used CIS-20 [54, 68], and one used the Fatigue Scale for children (FS-C), for adolescents (FS-A), for parents (FS-P), and for staff (FS-F) [50]. Three studies reported no impact of exercise intervention on fatigue [50, 54, 58], whereas two studies reported a significant reduced level of fatigue following the intervention [61, 68].

Other Outcomes

As summarized in Table **2**, intervention trials in small numbers of survivors have also included assessment of growth hormone and insulin-like growth factors [69], sleep duration and efficiency [50] health

knowledge, motivation for positive behavior changes, and practice of health behaviors [51, 66].

Limitations of Intervention Trials

Most trials had small sample sizes. All but three studies had 50 or fewer participations [49, 51, 67]. Trials differed in rates of recruitment, which ranged from 40% to 85% [49, 53, 55, 56, 58, 65, 67]. The primary reasons for refusal, as noted in one study [43], were lack of interest in health promotion and lack of time. This was in contrast to a previous study that recruited survivors who attended late-effect follow-up clinics to an intervention program aiming to improve knowledge about cancer treatment and increase the practice of healthy behaviors [70]. This study yielded an 86% participation rate. These results suggest that clinic-based trials may achieve a higher recruitment rate than those performed outside of the clinic setting, although there may be biases associated with this self-selected sample. The adherence rates (i.e., the percentage of subjects who successfully completed part or all of the scheduled sessions) also varied across trials. Some reported satisfactory adherence, ranging between 67 and 90% [50, 58, 61] whereas others reported low adherence (11%) [49] and high drop-out rates (44%) [64]. One study indicated that a major reason for drop-out was the frequency of training was too much for children who were also participating in other social activities [65]. The most common reported perceived barriers to improving exercise and dietary behaviors in 118 childhood cancer survivors aged 13-35 years old were fatigue, lack of time, lack of access to exercise equipment, taste preferences, availability of healthy foods, and influence of advertising [71]. For child and adolescent survivors, lack of parental support may also server an important barrier for exercise intervention as most parents regarded their child as very vulnerable and restricted physical activity to prevent potential harm [65].

Summary of Intervention Trials

The number of intervention trials utilizing exercise interventions in childhood cancer survivors has increased in recent years but is still limited. Many of these trials focused on feasibility and safety issues, both of which were generally confirmed. Findings from these trials on outcomes specifically related to exercise as well as health-related outcomes are mixed. Very few trials designed to influence diet in childhood cancer survivors exist, although results suggest that survivors may be amenable to dietary changes designed to promote health.

CONCLUSION

A growing body of literature suggests that a high proportion of childhood cancer survivors do not meet the physical activity guidelines and have poor adherence to existing dietary guidelines. A number of recent intervention trials have evaluated the effect of lifestyle intervention on physical fitness, muscle strength, physical function and psychosocial outcomes. Although findings from these studies are preliminary due to small sample size of the trials, the existing evidence consistently suggest that exercise intervention is safe and feasible for patients and survivors of childhood cancer. Childhood cancer survivors should be encouraged to engage in physical activity, adapt a healthy diet, and keep a healthy weight throughout the survivorship. Prospective observational studies are needed and should adopt validated methods to assess diet and physical activity and when possible should incorporate objective measures such as biomarkers. More adequately powered intervention trials are needed and should ideally adopt a randomized controlled design. Intervention trials should be designed to assess diet and physical activity as individual or combined programs. Like interventions in the general population, the sustainability of behavior change and long-term effects on weight and health should be assessed. In survivors, cancer-related endpoints such as cancer recurrence and survival remain of high priority. Evidence-based approaches should be used to guide future development of nutrition and physical activity guidelines for childhood cancer survivors.

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