Pre-habilitation- Promoting Exercise in Adolescent and Young Adult Cancer Survivors for Improving Lifelong Health- A Narrative Review

Margaux J. Barnes PhD; Eric P. Plaisance, PhD; Lynae Hanks PhD, RDN; Krista Casazza PhD, RDN

1601 4th Ave S, CPP I 310, University of Alabama at Birmingham, Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, Birmingham, Alabama, 35233, US

901 13th Street South, University of Alabama at Birmingham, Department of Human Studies, Birmingham, Alabama, US

Station 6385, Bloch 109, University of Montevallo, Department of Kinesiology, Montevallo, Alabama, 32115, US

Corresponding Author
Krista Casazza PhD, RDN
1601 4th Ave S, CPP I 310, University of Alabama at Birmingham, Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine, Birmingham, Alabama, 35233, US
kcasazza@peds.uab.edu

Abstract
Given the crucial role of exercise in the enhancement of cancer survivors’ long-term health and wellbeing, the aim of the current paper is to review what is known regarding the physiological mechanisms underlying treatment for cancer in adolescent and young adults (AYAs), summarize the interventions that have been implemented to date to increase AYA survivor exercise, and provide recommendations for specific strategies to promote exercise engagement with consideration of developmental issues relevant to AYA survivors. As musculoskeletal function is among the greatest determinants of...
morbidity and mortality across the life course, and the strength-structural properties of
the musculoskeletal system are largely established in adolescence and young adulthood,
perturbations during this time may have profound implications as AYA survivors age.
While evidence exists supporting interventions delivered at any time point in the cancer
journey, the most effective interventions may be those implemented prior to the onset of
late effects or noted declines in key health behaviors. Targeting adolescents is of vital
importance as physical activity in AYAs continues to decline with age and onset of
chronic conditions. As an endocrine organ, contractions of skeletal muscle via resistance
exercise exert indirect effects on overall metabolic pathways via the paracrine and
endocrine effects of skeletal muscle and direct effects via muscle hypertrophy. By
intervening at an earlier stage of survivorship, prior to the onset of many late effects, and
by providing supervised strength training with immediate feedback to survivors,
interventions may be associated with increased efficacy in the mitigation of long-term
health risks.

Keywords: Resistance training; adolescent and young adult cancer survivors; physical
activity; comorbidities; lean body mass

Introduction

While advances in medical treatments have increased survival rates above 80% in
adolescent and young adults (AYAs), cancer and its associated treatment increases risk
for long-term morbidity and mortality (1). The mortality rate in AYA survivors due to
cancer recurrence, secondary cancers, and cardiovascular and lung disease as a result of
their original diagnosis and subsequent treatment greatly surpasses rates seen in the
general population and survivors of cancer diagnosed later in life (2-4). AYA cancer
survivors also report a significantly higher prevalence of adverse physiologic and
psychosocial outcomes including obesity, cardiovascular disease (CVD), hypertension,
diabetes, osteoporosis, asthma, disability, and mood issues compared to peers without a history of cancer (5-7).

Given the known risks for increased mortality and morbidity, fostering the development of healthy lifestyle behaviors designed to target specific late effects early in life is crucial for healthy aging in AYA cancer survivors. Exercise is particularly important in the mitigation of late effects as it alters metabolic pathways that ultimately influence the development of chronic diseases associated with cancer treatment. In both the general population and cancer survivors specifically, the benefits of engagement in regular exercise is well-documented and includes (but is not limited to) increased cardiorespiratory fitness, maintenance of muscle and bone strength, reduced anxiety and depression, reduced risk of some future cancers, and more favorable cardiovascular and metabolic profiles (8-12).

Despite the increased need for adequate exercise, a significant proportion of AYAs with a history of cancer do not meet the Centers for Disease Control and Prevention’s (CDC) recommended weekly minimum of 150 minutes of moderate to vigorous intensity exercise (13). In fact, it is estimated that 48 to 65% of AYA survivors are currently not meeting these recommendations, regardless of cancer diagnosis (5, 14). The only study identified to document patterns of exercise engagement in AYA survivors across the cancer experience found that while 70% of AYA in the sample met CDC recommendations prior to treatment, only 10% reported meeting guidelines during treatment, and less than 49% reported meeting exercise guidelines as survivors. Even though there was an increase in survivors who reported adequate exercise after treatment compared to during treatment, the total time spent exercising remained significantly
lower than pre-diagnosis activity (15). While rates of inactivity are similar to those seen in healthy adolescents and young adults, the lack of adequate exercise in the AYA survivor population has significant clinical importance and may contribute to survivors’ already heightened risk for increased morbidity and mortality (16). Given the crucial role of exercise in the mitigation of survivors’ long-term health and wellbeing, the aim of the current paper is to review what is known regarding the physiological mechanisms underlying treatment for cancer in AYA and pediatric cancer populations, summarize the interventions that have been implemented to date to increase AYA survivor exercise, and provide recommendations for specific strategies to promote exercise engagement with consideration of developmental issues relevant to AYA survivors.

**Physiological Mechanisms Underlying Inadequate Physical Activity (PA) and Survivor Health**

The decline of lean body mass (LBM) at diagnosis and during treatment in patients stresses the relevance of diminished PA, often combined with the presence of negative energy balance and skeletal muscle cachexia. Furthermore, treatment with corticosteroids and some chemotherapeutic agents can cause muscle protein catabolism, which can in turn decrease LBM and increase adiposity and insulin-resistance. It is worth noting that similar patterns of loss of LBM have been demonstrated in cancer patients regardless of whether they were treated with corticosteroids or chemotherapeutic agents associated with cachexia (17-20). This might indicate that decreased PA plays a critical role in the sustained low levels of LBM in AYA survivors.
Research indicates that AYAs have a higher than expected prevalence of frailty, suggesting the potential for accelerated aging. Applying the frailty assessment developed by Fried et al (21) for older adults, Ness et al (20) report prevalence of frailty (an assessment which includes any three of the following: low lean mass, self-reported exhaustion, low energy expenditure, slowness, weakness) was 2.7% among male participants and 13.1% among female participants. Pre-frailty (includes any two of the frailty measures) was present among 12.9% of men and 31.5% of women. The prevalence for frailty and pre-frailty increased with age and in females which is explained at least in part by differences in LBM. In addition, self-reported exhaustion and low energy expenditure were highly prevalent in groups with or without frailty. Ness also found that risk of death among those who were frail was 2.6-fold greater than those who were not frail (22). Importantly, even in the absence of overt non-cancer assessments, many AYA survivors report symptoms that interfere with activities of daily living (4, 19, 23-25). The interference is often integrated with musculoskeletal health, precedes the onset of chronic disease and is a predictor of early mortality (1, 26-29). In particular, two major musculoskeletal complications are prevalent: musculoskeletal pain and growth failure. Further, disturbed gait, fractures, kyphosis, lordosis, and growth failure have been well-documented and osteopenia/osteoporosis has been observed in all phases of the disease: at diagnosis, during treatment, and throughout the post-treatment period for as long as 20 years (30). An increased fracture frequency has also been described (26, 30-32) demonstrating the fracture rate in young AYAs six times that of healthy controls (33, 34).

Substantial evidence in animals and humans highlights the detrimental effects of physical inactivity across systems emanating from poor musculoskeletal development in
“healthy” states that would undoubtedly be augmented in the pro-inflammatory environment of cancer treatment. For example, just one to three weeks of bed rest in otherwise healthy, active young men had a more profound impact on physical work capacity than did three decades of aging in the same men (35, 36). Within days, bed rest led to decreased skeletal muscle insulin sensitivity, impaired fitness, and lower leg muscle mass (37). Impaired insulin signaling, altered glucose and lipid metabolism and increased central adiposity were also noted. While bed rest is an extreme model of inactivity and does not accurately mimic low levels of physical activity seen in AYA survivors, the findings are germane to AYA survivors and the potential musculoskeletal and metabolic late effects they may have accrued as a result of their diagnosis and treatment (38). Specific to young adult survivors of cancer, AYAs show accelerated aging, poorer physical fitness and muscle function, and decreased bone mineralization related to their disease and treatment as well as inadequate physical activity (22, 31, 39, 40). The manifestations of many of the co-morbidities observed in AYA survivors have been directly linked to the aforementioned decline in musculoskeletal function.

Adolescence represents the greatest capacity for satellite cell proliferation and differentiation when activated gives rise to myoblasts that fuse muscle fibers to the skeleton and are integral in establishing strength-structural properties of the musculoskeletal system (37). Physical activity is central to this principle given that the availability of nutrients across systems needed to permit necessary biological adaptations is catalyzed by endocrine and paracrine effects of muscle contraction. As musculoskeletal function is among the greatest determinants of morbidity and mortality across the life course, and the strength-structural properties of the musculoskeletal system
are largely established in adolescence and young adulthood, perturbations during this
time may have profound implications as AYA survivors age. Aging research
demonstrates that most of the declines in musculoskeletal function attributed to
chronological age are instead a result of physical inactivity (37). Along with an overall
reduction in mass, changes are occurring within the skeletal muscle to affect function.
Changes such as accumulation of intra- and extra-myocellular lipids, improper folding of
structural and contractile proteins, and mitochondrial dysfunction attenuate the regulatory
control of skeletal muscle on metabolic function (41). Biswas et al (42) recently reported
that in the general population the effect of sedentary time on all-cause mortality was
greater among those with low levels of physical activity compared with those with high
levels of physical activity. Despite the known relations between physical activity,
musculoskeletal function, and metabolic health during adolescence, connections have not
been established linking these variables to the design and implementation of interventions
aimed at increasing survivor physical activity.

**What has been done – A Review of the Literature**

To better understand the strategies used to increase exercise in AYA survivors to
date, a search was conducted for studies published prior to April 2015 in two databases:
Medline and PsychINFO. The search consisted of the subject headings and text words:
“adolescent cancer survivor”, “young adult cancer survivor”, or “AYA cancer survivor”
combined with each of the following: “health behaviors,” “exercise,” or “physical
activity,” and “intervention.” All search results were limited to English language. A
secondary search was conducted by manually reviewing the reference sections of
identified studies and review articles. After obtaining all relevant manuscripts, abstracts
were screened to ensure applicability to the topic. Manuscripts were included if they (1) were empirical studies reporting on an intervention designed to promote exercise or physical activity for participants either receiving treatment for or a survivor of cancer; (2) included adolescents between the ages of 11 and 18 or young adults between the ages of 18 and 29; and (3) included a sample size of at least 10 participants. Observational studies (including case reports, case-control studies) and surveys were excluded from this review.

The literature search, including primary and secondary search strategies, yielded 463 articles. Following a review of titles and abstracts and taking into account duplicate search returns, the search was narrowed to 22 papers that appeared to meet the inclusion criteria described above. Careful readings of the 22 full manuscripts further reduced the field to 9 studies that met all inclusion criteria. Of these studies, six included adolescent survivors, two addressed young adult survivors only, and one included both adolescent and young adult survivors. Interventions were heterogeneous across study design (non-randomized, non-controlled versus randomized, controlled trial), sample sizes (range = 10 – 251), ages (range = 3 – 39 years of age), diagnoses (acute lymphoblastic leukemia (ALL), brain tumor, mixed diagnoses), and points of intervention (on-treatment, immediate post-completion of treatment, long-term survivorship) (Table 1).

Of the studies including adolescents, four included survivors only (aged 6-39 years), one included on-treatment participants only (aged 3-17 years), and one included youth diagnosed with cancer regardless of treatment status (aged 14-18 years). No adverse events or perceived risks were reported in any of the studies regardless of intervention timing or treatment status suggesting that exercise interventions are safe and
appropriate from a medical standpoint for this population.

For those studies targeting exercise in adolescent survivors, five of the six interventions showed significant improvement in outcomes related to exercise following completion of the intervention however no interventions evaluated outcomes based on the individual strategies comprising the intervention (14, 43–45). Four of the interventions also involved trained interventionists to ensure participant adherence with the intervention, including a mix of supervised instruction and unsupervised exercise sessions allowing adolescents to practice learned skills at home (43, 46–48). Intervention duration varied from four days to 24 months with no apparent association between length of intervention and positive change in exercise outcomes. While initial gains were noted in five of the six interventions, only the 4-day adventure-based exercise promoting intervention by Li et al measured long term outcomes, demonstrating long-term success through the maintenance of exercise-promoting cognitions (i.e. exercise self-efficacy) gains at 9-month follow-up (48). Of note, the one study that did not show improvements in exercise outcomes was comprised of a single psychosocial strategy, goal-setting, and, while activity was encouraged, strategies focused on active exercise engagement were not included (39, 40).

Two interventions included young adult survivors (49, 50). Rabin and colleagues conducted a 12-week internet-based exercise intervention guided by Social Cognitive Theory and the Transtheoretical Model of Behavior Change with 18 young adult cancer survivors (49). The intervention used psycho-education, goal-setting, and self-monitoring to increase exercise via a web-based exercise manual matched to participants’ stage of readiness to engage in exercise. Feasibility and participant satisfaction were high and
self-reported outcomes indicated that exercise, mood, and fatigue were significantly improved following the intervention compared to the control group. Adherence and long-term maintenance of outcomes were not measured limiting the ability to draw conclusions about the intervention’s efficacy. Again, the intervention focused solely on cognitions and behaviors that may promote engagement in exercise rather than specific exercise techniques and strategies, limiting the conclusions that can be drawn in relation to survivor health benefits.

Valle and colleagues conducted a similar 12-week intervention with 86 young adult survivors using a Facebook-based program called FITNET aimed to increase moderate-to-vigorous exercise (50). The intervention utilized psycho-education, goal-setting, self-monitoring, and social support to promote self-efficacy for exercise. Self-report outcome measures included exercise frequency and amount, self-efficacy for exercise, social support for exercise, and self-monitoring of exercise. Interestingly, the intervention group showed lower self-efficacy for exercise and social support from online friends compared to the control group. No gains in moderate to vigorous exercise were found based on the intervention, though social support and self-efficacy were positively associated with moderate to vigorous exercise across both groups (50). Again, engagement in individual exercise promoting strategies across the intervention was not analyzed.

Lastly, the intervention delivered to both adolescents and young adults implemented a 16-week home-based exercise program to 17 survivors of ALL between the ages of 16 and 30 years (27). The home exercise program consisted of 3-4 days per week of strength exercises and aerobic exercise three times per week of the survivor’s
choice for 30 minutes or more. Self-monitoring was encouraged to track daily engagement in exercise. Additionally, problem-solving skills training was provided by a counselor twice weekly via telephone to increase motivation and maintain survivors’ engagement in the exercise program. Results indicated that immediately following the intervention, fasting insulin, insulin resistance, waist circumference, waist-to-hip ratio, percent fat, and supine diastolic blood pressure significantly decreased. These outcomes were supported by concurrent improvements in fitness including peak oxygen uptake and muscle strength (in abdominals, lower back and leg). Long-term maintenance of physical activity and related outcomes were not assessed.

Where do we go from here?

While the literature to date provides promising preliminary evidence for the feasibility and benefits of exercise interventions in AYA survivors, specific limitations of the interventions conducted thus far must be considered. First, and perhaps most importantly in the context of the current review, the individual strategies comprising the interventions varied widely, both in type, number of strategies employed, and delivery method. Further, with the exception of the study conducted by Jarvela and colleagues (27), no studies have linked specific exercise strategies to musculoskeletal or metabolic outcomes. Knowledge of the direct and indirect effects of exercise strategies on the physiological pathways associated with the late effects of cancer is critical in the development of efficacious interventions for AYA survivors.

Exercise Strategies to Promote Health in AYAs
Abdominal adiposity, lower skeletal muscle mass and deteriorated metabolic risk profile underscore the heightened health risk of AYA survivors. Additionally, decline in skeletal muscle mass and function has been identified as a significant risk factor for mortality, even after controlling for other risks factors such as tumor stage and type of chemotherapy (4, 15, 20, 22). Current recommendations indicate physical activity is a priority for AYA survivors with an emphasis on moderate to vigorous aerobic activity. While aerobic exercise produces numerous metabolic benefits and provides a potent physiological stimulus that perturbs the equilibrium of multiple organ systems, the physiological adaptations elicited by aerobic training are unique from those elicited by resistance training (51). The specific mechanisms of each form of training are presented below.

**Physiological Mechanisms of Strength Training.**

Specific biology and pathophysiology of this process are beginning to be understood, yet translation for formal assessment and intervention is still lacking. Physical performance among AYAs resembles that expected with long-term age-related changes such that cardiopulmonary fitness and hand grip strength values are lower among AYAs than among age-matched, sex-matched, and race-matched peers, yet similar to values expected among older adults (in their 60s) (15, 19, 20). As an endocrine organ, skeletal muscle is integrally involved in the synthesis and releases of proteins with well-established roles in regulating various metabolic pathways. However, the well-known beneficial effects of these “myokines,” are contraction dependent, with the requisite force needing to be above that which is encountered on an everyday basis (i.e., overload) (35, 36). In addition, oxidative metabolism is the dominant source of energy for skeletal
Because blood flow and oxygen delivery are associated with workload and oxygen demand to contracting muscle, physical inactivity accelerates age-related changes in structural alterations, loss of LBM and overall decreased musculoskeletal function.

The metabolic changes identified in aging suggest hemodynamic and metabolic impairments, including attenuated release of ATP and blood flow adversely influencing nutrient delivery and utilization can be mitigated by muscle contraction (52). Translating the well-described adverse effects of physical inactivity in aging to the accelerated effects of aging and frailty (20) in childhood cancer survivors for intervention is highly relevant. Interestingly, release of lactate from skeletal muscle (anaerobic metabolism) has been shown to compensate for lower oxidative metabolism even when impaired mitochondrial and contractile efficiency exists (41).

**Physiological Mechanisms of Aerobic Training.**

The long-term sequelae which increases prevalence and severity with advancing age and consequential reduced life expectancy, could be mitigated by aerobic exercise. Aerobic exercise has the potential to exert increases physical function, quality of life, cancer-related fatigue and ultimately enhance survival (53). Unlike that which is demonstrated in the general population, the RCTs and CCTs, to date have not provided convincing evidence for benefit in AYAs. It is likely that the decrements in cardiorespiratory fitness (54), lower oxygen capacity (55) and system wide markers of reduced physiologic capacity, particularly in conjunction cardiotoxic treatment regimens (54) limit adherence to moderate intensity aerobic training. AYAs struggle to return to premorbid cardiorespiratory fitness conditions (15). Times on the six minute walk test have demonstrated a 1.3 standard deviations less than expected and/or times equivalent to...
those aged 20-30 years older among AYAs (18). In addition, newly diagnosed children performed significantly lower than their peers on the six-minute walk test yet there were no differences in groups based on cycle of treatment (phase 1 vs 3) suggesting cardiorespiratory fitness in AYAs extends beyond lower physical inactivity among this population (18). The chronicity of muscle weakness, decline in cardiorespiratory fitness (56, 57) and increased oxidative stress, typical side effects of treatment (17) exacerbate the decrements in cardiorespiratory fitness. An additional complexity is that, one in three AYAs are overweight at least in part due to late effects of treatment (15). AYAs are often observed to have chronic musculoskeletal limitations (31). Thus it is conceivable, the physiologic phenotype, preceding chronic disease risks including changes in neuromuscular control, muscular performance, energy metabolism and decline in physiologic reserve (20), limits the expectation of achieving aerobic exercise associated with benefits somewhat unrealistic in AYAs (58). We contend that in an effort to improve overall health resistance training method may be more appropriate when the improvement of lean mass, and optimizing aerobic fitness and muscle strength in an effort to engage in an aerobic fitness program in AYAs. Subsequently, aerobic exercise training methods may be more effective in maintenance of body weight and body composition as well as sustaining metabolic health.

Collectively, resistance training appears to be essential as an effective therapy to influence long-term health in AYAs. As an endocrine organ, contractions of skeletal muscle via resistance exercise exerts indirect effects on overall metabolic pathways via the paracrine and endocrine effects of skeletal muscle and directly via muscle hypertrophy (52). In response to the demand for ATP, skeletal muscle contractility
substantially increases cellular oxidative capacity, blood perfusion, and extracellular matrix components. Resistance exercise is an anaerobic activity that almost exclusively relies on blood glucose as a fuel source during exercise and uses fats in recovery to regenerate ATP (52). This is important as it creates a metabolic sink effect thereby improving insulin sensitivity and fat metabolism, each of which are known to exhibit impairments in cancer survivors (59). Although the basic physiologic response to resistance exercise is skeletal muscle hypertrophy, farther-reaching metabolic effects in survivors have not been adequately explored.

**Recommendations.**

**Exercise Strategy.** As lean mass stands as a marker of better overall health and can be associated with longer survival (27, 59, 60), development of exercise programs should focus on the optimization of musculoskeletal health rather than the dogmatic approach of adipose tissue reductions. Specifically, progressive muscle loading via resistance training, facilitates increases in stress to confer continued physiological adaptation of the exercise itself. To learn proper form and technique we recommend qualified professional trainers to provide instruction and attentive supervision at least in initial sessions.

Progressive training should include eccentric, isometric and concentric components with free weights and resistance equipment. One-to-two minutes of rest should be incorporated between sets. A cool down with less intense activities and static stretching should follow each training session. The lower perceived exertion and more immediate changes in strength (and body composition), as well as less requisite energy expenditure associated with strength training may make resistance training forms of exercise more acceptable as an initial behavioral change to increase exercise when cardiovascular
fitness may be low. If possible, in an effort to quantify observable changes in body composition and demonstrate the potential effectiveness of exercise training, body composition assessment may be considered. Documentation of the more immediate, observable gains in body composition has been shown to promote greater adherence thus maximizing long-term health benefits. Strength testing can encompass elbow flexion and knee extensors performed unilaterally on both appendages. These tests have been validated as valuable indices of muscle performance and mobility status and have proven to be sensitive to resistance training. These exercises should not be a part of strength training program to limit muscle learning effect and offer a more reliable estimate of improved strength. Handgrip strength using a dynamometer can also be used. Resistance training may also be more beneficial than aerobic training for patients who are underweight (due to treatment, loss of muscle mass, etc.).

**Intervention Delivery.**

While evidence exists supporting interventions delivered at any time point in the cancer journey, the most effective interventions may be those implemented prior to the onset of disease or noted declines in key health behaviors. While the adolescent survivor may have already experienced the development of some late effects and declines in exercise behaviors, the full development and/or detrimental effects of late effects and sedentary behavior may not be realized and thus are still modifiable in terms of mitigation of long-term metabolic risk. Initial changes in neuromuscular control, mechanical performance, and energy metabolism are subtle and are not associated with noticeable loss of function during daily life. Targeting adolescents is of vital importance as physical activity in AYAs continues to decline with increasing age and onset of
chronic conditions (9, 11, 19-21). As such, by intervening at an earlier stage of survivorship, prior to the onset of chronic disease, and by providing supervised strength training with immediate feedback to survivors, interventions may be associated with increased efficacy in the mitigation of long-term health risks. Taken together, the prevention of musculoskeletal impairment and decline in metabolic control, as well as enhancement of health-related quality of life requires a system that promotes cost-effective strategies, not only for serious diseases amenable to early detection and treatment, but also a system that incorporates intervention for early deficits in metabolic control, muscle strength, and energy metabolism.

Conclusions.

A better understanding of how to capitalize on growth and development of skeletal muscle has the potential to influence interventions that in turn could influence the long-term health and wellbeing of AYA cancer survivors. While not all late effects will be responsive either in reversal or mitigation of impact to exercise, the metabolic, cardiovascular, and musculoskeletal late effects seen in a significant proportion of AYA survivors would likely show improvement following exercise. AYA survivors have a substantially higher BMI than the “standard reference population”, and as a consequence, interventions have attempted to modify behavior through weight loss. However, improving metabolic and musculoskeletal health in the absence of weight loss as well as in survivors who are "metabolically obese” but may not yet be phenotypically obese (their underlying biology reflects the effects of obesity without excess weight) will have far-reaching effects across domains including survivor short and long-term health, healthcare utilization, and overall economic burden related to survivorship. Specifically,
The question of bio-behavioral mechanisms and pathways through which endocrine and paracrine effects of skeletal muscle function may improve metabolic control (glucose/lipid metabolism) in AYAs must be explored. We know that muscle is impaired by cancer and its treatment with early onset “frailty” as a consequence. A specifically tailored resistance training program offers an avenue for therapeutic modification with the prospect of enhancing musculoskeletal health and improving quality of life in this population.
References


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59. Nottage KA, Ness KK, Li C, Srivastava D, Robison LL, Hudson MM. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic

Conflict of interest

“The authors declare that they have no competing interests”.
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<th>Publication</th>
<th>Assessment Points</th>
<th>N, age</th>
<th>Cancer Diagnosis</th>
<th>Design/Methods</th>
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<td>Gilliam et al., 2011&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Baseline and post-intervention</td>
<td>12, 6 - 18 y Off-treatment at least 12 months</td>
<td>ALL and Brain Tumor</td>
<td>Non-randomized, non-controlled pilot study evaluating 6-session exercise intervention; fitness assessment and caregiver/self-report QoL</td>
<td>SCT In vivo training, Behavioral reinforcement, Self-monitoring</td>
<td>Adherence variable, though efficacy was demonstrated through significant changes in endurance (P&lt;0.02), strength (P&lt;0.047), and functional mobility (P&lt;0.44).</td>
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<td>Hartman et al., 2009&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Dx (baseline), 4 mth post-dx, 12 mth post-dx, 24 mth post-dx, and 12 mth post-tx</td>
<td>51, 3 - 17 y On-treatment</td>
<td>ALL</td>
<td>Randomized, controlled trial of 2-year exercise program; Anthropometric data, body composition, bone mineral density, fitness assessment</td>
<td>None In vivo training, Psycho-education, Self-monitoring</td>
<td>Adherence variable. Body fat increased equally during treatment (P=0.69) however 1 year post-treatment showed more rapid decline of excess body fat in intervention group (P=0.013). Lean body mass, bone mineral density, and fitness of both groups decreased equally during treatment (all P &gt; 0.16), likely related to adherence with intervention.</td>
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<td>Huang et al., 2014&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Baseline and post-intervention</td>
<td>38, 8-18 y Off-treatment at least 2 years</td>
<td>ALL</td>
<td>Randomized, controlled trial of 4 month web, phone, and text message delivered weight management intervention; Objective and self-report assessment</td>
<td>None Psycho-education, Problem-solving skills training; Social support</td>
<td>Intervention adolescents aged 14 and older showed less weight gain (P=0.05) and increased MVPA (P&lt;0.01) compared to controls. All intervention participants reported reduced negative mood (P&lt;0.05) compared to controls. Adherence not measured though receipt of curriculum greater in intervention group (80%) vs control group (50%).</td>
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<td>Hudson et al., 2002&lt;sup&gt;29&lt;/sup&gt;; Cox et al., 2005&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Baseline and 1 year follow-up</td>
<td>251, 12 – 18 y Mean time since dx = 10.6 y</td>
<td>Mixed</td>
<td>Randomized, controlled behavioral intervention study; Self-report</td>
<td>Health Belief model Goal-setting</td>
<td>No significant improvements in survivor-selected health behavior goals related to exercise (P&gt;0.10).</td>
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<td>Study</td>
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<td>Keats &amp; Reed, 2008&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Baseline, Mid-intervention, Post-intervention, and 3 and 12 month follow-up</td>
<td>Mixed</td>
<td>Non-randomized, non-controlled pilot study; 16-week group physical activity and educational intervention; Self-report and objective fitness assessment</td>
<td>Increased endurance (P=0.03), upper body strength (P=0.04), flexibility (P&lt;0.03), QOL (P=0.01), and improved general fatigue (P=0.01) documented across the 16-week intervention; however, only overall QOL gains (P=0.05) maintained over 12-month follow-up. Adherence 81.5% suggesting the group intervention is a feasible.</td>
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<td>Li et al., 2013&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Baseline and 3, 6, 9 months post-intervention</td>
<td>Mixed</td>
<td>Randomized, controlled trial evaluating effectiveness of a 4-day physical activity promoting intervention; Self-report</td>
<td>Intervention group reported increased readiness for PA (P&lt;0.001), higher PA levels (P&lt;0.001), and higher self-efficacy (P=0.04) compared to controls. 9 mth post-intervention evaluation indicated survivors maintained increases in PA (P&lt;0.001), self-efficacy (P&lt;0.001), and QoL(P&lt;0.001).</td>
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<td>Rabin et al., 2011&lt;sup&gt;43&lt;/sup&gt;</td>
<td>18, 18 – 39 y Mean time since dx = 4.03 y</td>
<td>Mixed</td>
<td>Randomized, controlled trial of 12 week internet-based PA intervention; Feasibility assessment and self-report measures of PA and mood</td>
<td>Feasibility assessment indicated satisfactory participant satisfaction (71%) and feasibility (100% reported very easy website access; 86% reported easy to understand content). Effect size estimates were medium for PA (d=0.64) and large for mood (d=0.80).</td>
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<td>Valle et al., 2015&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Baseline and post-intervention</td>
<td>Mixed</td>
<td>Randomized, controlled 12-week facebook-based intervention to increase MVPA; Self-report PA and psychosocial outcomes</td>
<td>No significant changes in MVPA, self-monitoring, or social support (peer or family) based on intervention. Self-efficacy for PA decreased in intervention group (P=0.031). In total sample, social support (P=0.0003) and self-monitoring (P=0.004) were associated with increase in MVPA. Family support negatively associated with PA (P=0.046).</td>
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### Adolescent and Young Adults

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<th>Jarvela et al., 2012&lt;sup&gt;22&lt;/sup&gt;</th>
<th>Baseline and post-intervention</th>
<th>Mean time since dx = 10.6 y</th>
<th>Non-randomized, non-controlled study evaluating 16-week home-based exercise program; Peak oxygen uptake, muscle strength, and metabolic risk factors</th>
<th>None</th>
<th>Fasting plasma insulin (P=0.01), insulin resistance (P=0.002), waist circumference (P=0.003), waist-to-hip ratio (P=0.002), fat percent (P=0.04), and supine diastolic blood pressure (P=0.03) decreased while weight and body mass index remained unchanged. Peak oxygen uptake (P=0.01), maximal workload (P=0.002), and muscle strength (all P's &lt; 0.01) also significantly increased.</th>
</tr>
</thead>
</table>

Dx, diagnosis; Tx, treatment; y, years; mth, month; PA, physical activity; ALL, Acute Lymphoblastic Leukemia; QoL, Quality of Life; PT, physical therapy; SCT, Social Cognitive Theory; TPB, Theory of Planned Behavior