Review

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

[1]Margaux Barnes; [2]Eric Plaisance; [3]Lynae Hanks; [1]Krista Casazza

[1] University of Alabama at Birmingham, Department of Pediatrics, Division of General Pediatrics and Adolescent Medicine. 1601 4th Ave S, CPP I 310, Birmingham, Alabama, 35233, US.
[2] University of Alabama at Birmingham, Department of Human Studies. 901 13th Street South, Birmingham, Alabama, US
[3] University of Montevallo, Department of Kinesiology, Station 6385, Bloch 109, Montevallo, Alabama, 32115, US

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

Citation: Margaux Barnes, et al. Pre-habilitation- Promoting Exercise in Adolescent and Young Adult Cancer Survivors for Improving Lifelong Health - A Narrative Review. *Cancer Research Frontiers*. 2016 Feb; 2(1): 22-32. doi: 10.17980/2016.22

Competing Interests: The authors declare that there are no competing interests.
Received Oct 30, 2015; Revised Dec 18, 2015; Accepted Dec 29, 2015. Published Jan 21, 2016

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 cancer populations, summarize the interventions that have been implemented to-date to increase AYA survivor exercise participation, 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 AYA cancer patients and survivors have a higher than expected prevalence of frailty, suggesting the potential for accelerated complications with 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 LBM, self-reported exhaustion, low energy expenditure, slowness, weakness) was 2.7% among male participants and 13.1% among female participants. Pre-frailty (characterized as reporting 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 cancer 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 AYA cancer patients and survivors 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 cancer survivors, the findings are germane to this population 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, adolescents 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 cancer survivors have been directly linked to the aforementioned decline in musculoskeletal function.

Adolescence represents a period in which there is the greatest capacity for cellular proliferation and differentiation of satellite cells. When activated, satellite cells give rise to myoblasts. In turn, myoblasts 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. In fact, aging research demonstrates that most of the declines in musculoskeletal function are a result of physical inactivity rather than what is commonly attributed to chronological age (37). Along with an overall reduction in mass, changes occur 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 metabolic control of skeletal muscle (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 (in)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 physical activity or reducing physical inactivity.

What has been done – A Review of the Literature

To better understand the strategies used to increase exercise in AYA cancer 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 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 cognition (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 of the survivor's choice three times per week for 30 minutes or more per session. 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 cancer survivors, specific limitations of the interventions conducted thus far must be considered. First, and perhaps most important 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, decreased skeletal muscle mass and deteriorated metabolic risk profile underscore the heightened health risk of AYA cancer 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 AYA cancer survivors resembles that expected with long-term age-related changes such that cardiopulmonary fitness and hand grip strength values are lower among AYA survivors 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 muscle. 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.

Age-related hemodynamic and metabolic impairments (e.g., attenuated release of ATP and blood flow) 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 sequalae 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 improved 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

Table I. Empirical Studies Evaluating Exercise Interventions in Adolescent and Young Adult Cancer Survivors

Age (y)	Cancer Dx	Design/Methods	Theoretical Orientation and Strategies	Primary Results	Ref
Adolescents Only					
6 - 18	Mixed	Pilot study evaluating 6-session exercise intervention; fitness assessment and caregiver/self-report assessment	SCT In vivo training, Behavioral reinforcement, Self-monitoring	Adherence variable; significant improvement in endurance, strength, and functional mobility	14
3 - 17	ALL	Randomized, controlled trial of 2-year exercise program; Anthropometric data, body composition, bone mineral density, fitness assessment	None In vivo training, Psycho-education, Self-monitoring	Adherence variable; body fat increased equally during txt; But 1 yr post-tx showed more rapid decline LBM, bone mineral density, and fitness decreased	43
8-18	ALL	Randomized, controlled trial of 4 month web, phone, and text message delivered weight management intervention; objective and self-report assessment	None Psycho-education, Problem-solving skills training; SS	Less weight gain and increased MVPA; improved mood	44
12 – 18	Mixed	Randomized, controlled behavioral intervention study; self-report assessment	Health Belief model Goal-setting	Not improvement	46,47
14 – 18	Mixed	Non-randomized, non-controlled pilot study; 16-week group physical activity and educational intervention; self-report and objective fitness assessment	TPB In vivo training, Psycho-education, Self-monitoring, Goal-setting, SS	Increased endurance, upper body strength, flexibility, QOL, and improved general fatigue; overall QOL gains maintained over 12-mth FU; 81.5% adherence	45
9 - 16	Mixed	RCT evaluating effectiveness of a 4-day PA promoting intervention; self-report assessment	TTM Psycho-education, Goal-setting	Increased readiness for PA, higher PA levels, and higher self-efficacy. 9 mos post-intervention evaluation	48
Young Adults Only					
18 – 39	Mixed	RCT of 12 week internet-based PA intervention; feasibility study; self-report assessment	SCT and TTM Psycho-education, Goal-setting, Self-monitoring	Intervention satisfaction and feasibility observed; effect size estimates were medium for PA and large for mood	49
21 – 39	Mixed	12-week RCT Facebook-based intervention to increase MVPA; self-report assessment	SCT Psycho-education, Goal-setting, Self-monitoring, SS	No significant changes in MVPA, self-monitoring, or SS (peer or family); self-efficacy SS and self-monitoring were associated with increase in MVPA; family support negatively associated with PA.	50
Adolescent and Young Adults					
16 - 30	ALL	Non-RCT evaluating 16-week home-based exercise program; peak oxygen uptake, muscle strength, and metabolic risk factors assessment	None Self-monitoring, problem-solving skills training	Insulin, insulin resistance, waist circumference, waist-to-hip ratio, fat percent, and blood pressure decreased.Weight and BMI unchanged; peak oxygen uptake, maximal workload, and muscle strength increased	40

Dx, diagnosis; Tx, treatment; y, years; mo, month; mos, months; PA, physical activity; MVPA, Moderate to Vigorous Physical Activity; ALL, Acute Lymphoblastic Leukemia; QOL, Quality of Life; PT, physical therapy; SCT, Social Cognitive Theory; SS, Social Support; TPB, Theory of Planned Behavior; TTM, Transtheoretical Model of Behavior Change 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 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 LBM, 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 LBM 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 the muscle 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 progressive training may make resistance exercise more acceptable as an initial behavioral change to increase cardiovascular fitness when energy may be low. Resistance training may also be more beneficial than aerobic training for patients who are underweight (due to treatment, loss of muscle mass, etc.). 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. Observable short-term gains in LBM and improvement 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. Handgrip strength using a dynamometer can also be used. These tests have been validated as valuable indices of muscle performance and mobility status and have proven to be sensitive to resistance training. Testing exercises should not be a part of strength training program to limit confounding by muscle learning effect, and thus offering a more reliable estimate of improved strength.

Intervention Delivery

While evidence exists supporting interventions initated 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 cancer-related impariments 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 AYA cancer patients and survivors 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 cancer-related effects can be reversed, potential mitigation may be conferred. Metabolic, cardiovascular, and musculoskeletal late effects have been noted in a significant proportion of AYA cancer survivors. Moreover, 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/adiposity) will have far-reaching effects across domains including 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 AYA cancer survivors must be explored. We know that muscle is impaired by cancer and its treatment modalities, evidenced by early onset "frailty." 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.

Abbreviations

ALL	Acute Lymphoblastic Leukemia;
AYA	Adolescent and Young Adults;
CCT	Clinical Control Trials;
CDC	Centers for Disease Control and Prevention;
CVD	Cardiovascular Disease;
LBM	Lean Body Mass;
MVPA	Moderate to Vigorous Physical Activity;
Mth	Month;
PA	Physical Activity;
PT	Physical therapy;
QOL	Quality of Life;
RCT	Randomized Control Trials;
SCT	Social Cognitive Theory;
TPB	Theory of Planned Behavior;
TTM	Transtheoretical Model of Behavior Change

References

1. Oeffinger KC, Tonorezos ES. The cancer is over, now what?: Understanding risk, changing outcomes. Cancer. 2011 May 15;117(10 Suppl):2250-7. DOI: 10.1002/cncr.26051.
2. Bhatia V, Arya V, Dabadghao P, Balasubramanian K, Sharma K, Verghese N, et al. Etiology and outcome of childhood and adolescent diabetes mellitus in North India. J Pediatr Endocrinol Metab. 2004 Jul;17(7):993-9.
3. Fossa SD, Aass N, Harvei S, Tretli S. Increased mortality rates in young and middle-aged patients with malignant germ cell tumours. Br J Cancer. 2004 Feb 9;90(3):607-12. DOI: 10.1038/sj.bjc.6601558.
4. Mertens AC, Brand S, Ness KK, Li Z, Mitby PA, Riley A, et al. Health and well-being in adolescent survivors of early childhood cancer: a report from the Childhood Cancer Survivor Study. Psychooncology. 2014 Mar;23(3):266-75. DOI: 10.1002/pon.3414.

5. Badr H, Paxton RJ, Ater JL, Urbauer D, Demark-Wahnefried W. Health behaviors and weight status of childhood cancer survivors and their parents: similarities and opportunities for joint interventions. J Am Diet Assoc. 2011 Dec;111(12):1917-23. DOI: 10.1016/j.jada.2011.09.004.
6. Bhatia SK, Bhatia SC. Childhood and adolescent depression. Am Fam Physician. 2007 Jan 1;75(1):73-80.
7. Tai E, Buchanan N, Townsend J, Fairley T, Moore A, Richardson LC. Health status of adolescent and young adult cancer survivors. Cancer. 2012 Oct 1;118(19):4884-91. DOI: 10.1002/cncr.27445.
8. Demark-Wahnefried W. Cancer survival: time to get moving? Data accumulate suggesting a link between physical activity and cancer survival. J Clin Oncol. 2006 Aug 1;24(22):3517-8. DOI: 10.1200/JCO.2006.06.6548.
9. Demark-Wahnefried W, Rogers LQ, Alfano CM, Thomson CA, Courneya KS, Meyerhardt JA, et al. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. CA Cancer J Clin. 2015 May-Jun;65(3):167-89. DOI: 10.3322/caac.21265.
10. Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, Grant B, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin. 2006 Nov-Dec;56(6):323-53.
11. Wolin KY, Colditz GA. Implementing chronic disease prevention amongst cancer survivors. J Intern Med. 2011 Jan;269(1):85-7. DOI: 10.1111/j.1365-2796.2010.02295.x.
12. Wolin KY, Colditz GA. Cancer and beyond: healthy lifestyle choices for cancer survivors. J Natl Cancer Inst. 2013 May 1;105(9):593-4. DOI: 10.1093/jnci/djt052.
13. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012 Jul-Aug;62(4):243-74. DOI: 10.3322/caac.21142.
14. Gilliam MB, Madan-Swain A, Whelan K, Tucker DC, Demark-Wahnefried W, Schwebel DC. Cognitive influences as mediators of family and peer support for pediatric cancer survivors' physical activity. Psychooncology. 2013 Jun;22(6):1361-8. DOI: 10.1002/pon.3140.
15. Murnane A, Gough K, Thompson K, Holland L, Conyers R. Adolescents and young adult cancer survivors: exercise habits, quality of life and physical activity preferences. Support Care Cancer. 2015 Feb;23(2):501-10. DOI: 10.1007/s00520-014-2446-2.
16. Surgeon General's report on physical activity and health. From the Centers for Disease Control and Prevention. JAMA. 1996 Aug 21;276(7):522.
17. Christensen JF, Jones LW, Andersen JL, Daugaard G, Rorth M, Hojman P. Muscle dysfunction in cancer patients. Ann Oncol. 2014 May;25(5):947-58. DOI: 10.1093/annonc/mdt551.
18. Henderson TO, Ness KK, Cohen HJ. Accelerated aging among cancer survivors: from pediatrics to geriatrics. Am Soc Clin Oncol Educ Book. 2014:e423-30. DOI: 10.14694/EdBook_AM.2014.34.e423.
19. Hovi L, Era P, Rautonen J, Siimes MA. Impaired muscle strength in female adolescents and young adults surviving leukemia in childhood. Cancer. 1993 Jul 1;72(1):276-81.
20. Ness KK, Armstrong GT, Kundu M, Wilson CL, Tchkonia T, Kirkland JL. Frailty in childhood cancer survivors. Cancer. 2015 May 15;121(10):1540-7. DOI: 10.1002/cncr.29211.
21. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001 Mar;56(3):M146-56.
22. Ness KK, Krull KR, Jones KE, Mulrooney DA, Armstrong GT, Green DM, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime cohort study. J Clin Oncol. 2013 Dec 20;31(36):4496-503. DOI: 10.1200/JCO.2013.52.2268.
23. Goldsby R, Chen Y, Raber S, Li L, Diefenbach K, Shnorhavorian M, et al. Survivors of childhood cancer have increased risk of gastrointestinal complications later in life. Gastroenterology. 2011 May;140(5):1464-71 e1. DOI: 10.1053/j.gastro.2011.01.049.
24. Haddy RI, Haddy TB. Lifetime follow-up care after childhood cancer. J Am Board Fam Med. 2010 Sep-Oct;23(5):647-54. DOI: 10.3122/jabfm.2010.05.100031.
25. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst. 2001 Apr 18;93(8):618-29.
26. Halton J, Gaboury I, Grant R, Alos N, Cummings EA, Matzinger M, et al. Advanced vertebral fracture among newly diagnosed children with acute lymphoblastic leukemia: results of the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) research program. J Bone Miner Res. 2009 Jul;24(7):1326-34. DOI: 10.1359/jbmr.090202.
27. Jarvela LS, Niinikoski H, Heinonen OJ, Lahteenmaki PM, Arola M, Kemppainen J. Endothelial function in long-term survivors of childhood acute lymphoblastic leukemia: effects of a home-based exercise program. Pediatr Blood Cancer. 2013 Sep;60(9):1546-51. DOI: 10.1002/pbc.24565.

28. Kirchhoff AC, Krull KR, Ness KK, Park ER, Oeffinger KC, Hudson MM, et al. Occupational outcomes of adult childhood cancer survivors: A report from the childhood cancer survivor study. Cancer. 2011 Jul 1;117(13):3033-44. DOI: 10.1002/cncr.25867.
29. Smith WA, Li C, Nottage KA, Mulrooney DA, Armstrong GT, Lanctot JQ, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Cancer. 2014 Sep 1;120(17):2742-50. DOI: 10.1002/cncr.28670.
30. Wasilewski-Masker K, Kaste SC, Hudson MM, Esiashvili N, Mattano LA, Meacham LR. Bone mineral density deficits in survivors of childhood cancer: long-term follow-up guidelines and review of the literature. Pediatrics. 2008 Mar;121(3):e705-13. DOI: 10.1542/peds.2007-1396.
31. Sala A, Talsma D, Webber C, Posgate S, Atkinson S, Barr R. Bone mineral status after treatment of malignant lymphoma in childhood and adolescence. Eur J Cancer Care (Engl). 2007 Jul;16(4):373-9. DOI: 10.1111/j.1365-2354.2006.00757.x.
32. Sala A, Webber CE, Morrison J, Beaumont LF, Barr RD. Whole-body bone mineral content, lean body mass, and fat mass measured by dual-energy X-ray absorptiometry in a population of normal Canadian children and adolescents. Can Assoc Radiol J. 2007 Feb;58(1):46-52.
33. Riccio I, Tirelli A, Gimigliano F, Iolascon G, Gimigliano R. Rehabilitative approach in patients with vertebral fragility fracture. Aging Clin Exp Res. 2013 Oct;25 Suppl 1:S109-11. DOI: 10.1007/s40520-013-0113-y.
34. van der Sluis IM, van den Heuvel-Eibrink MM. Osteoporosis in children with cancer. Pediatr Blood Cancer. 2008 Feb;50(2 Suppl):474-8; discussion 86. DOI: 10.1002/pbc.21407.
35. Hamilton MT, Hamilton DG, Zderic TW. Exercise physiology versus inactivity physiology: an essential concept for understanding lipoprotein lipase regulation. Exerc Sport Sci Rev. 2004 Oct;32(4):161-6.
36. Katzmarzyk PT, Barlow S, Bouchard C, Catalano PM, Hsia DS, Inge TH, et al. An evolving scientific basis for the prevention and treatment of pediatric obesity. Int J Obes (Lond). 2014 Jul;38(7):887-905. DOI: 10.1038/ijo.2014.49.
37. Sonne MP, Alibegovic AC, Hojbjerre L, Vaag A, Stallknecht B, Dela F. Effect of 10 days of bedrest on metabolic and vascular insulin action: a study in individuals at risk for type 2 diabetes. J Appl Physiol (1985). 2010 Apr;108(4):830-7. DOI: 10.1152/japplphysiol.00545.2009.
38. Saunders TJ. The health impact of sedentary behaviour in children and youth. Appl Physiol Nutr Metab. 2014 Mar;39(3):402. DOI: 10.1139/apnm-2013-0446.
39. Adamsen L, Andersen C, Midtgaard J, Moller T, Quist M, Rorth M. Struggling with cancer and treatment: young athletes recapture body control and identity through exercise: qualitative findings from a supervised group exercise program in cancer patients of mixed gender undergoing chemotherapy. Scand J Med Sci Sports. 2009 Feb;19(1):55-66. DOI: 10.1111/j.1600-0838.2007.00767.x.
40. Jarvela LS, Kemppainen J, Niinikoski H, Hannukainen JC, Lahteenmaki PM, Kapanen J, et al. Effects of a home-based exercise program on metabolic risk factors and fitness in long-term survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2012 Jul 15;59(1):155-60. DOI: 10.1002/pbc.24049.
41. Nyberg M, Hellsten Y. Reduced blood flow to contracting skeletal muscle in ageing humans: is it all an effect of sand through the hourglass? J Physiol. 2015 Jun 10. DOI: 10.1113/JP270594.
42. Biswas A, Mallick S, Purkait S, Gandhi A, Sarkar C, Singh M, et al. Treatment outcome and patterns of failure in patients of pinealoblastoma: review of literature and clinical experience from a regional cancer centre in north India. Childs Nerv Syst. 2015 Aug;31(8):1291-304. DOI: 10.1007/s00381-015-2751-1.
43. Hartman A, te Winkel ML, van Beek RD, de Muinck Keizer-Schrama SM, Kemper HC, Hop WC, et al. A randomized trial investigating an exercise program to prevent reduction of bone mineral density and impairment of motor performance during treatment for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009 Jul;53(1):64-71. DOI: 10.1002/pbc.21942.
44. Huang JS, Dillon L, Terrones L, Schubert L, Roberts W, Finklestein J, et al. Fit4Life: a weight loss intervention for children who have survived childhood leukemia. Pediatr Blood Cancer. 2014 May;61(5):894-900. DOI: 10.1002/pbc.24937.
45. Keats MR, Culos-Reed SN. A community-based physical activity program for adolescents with cancer (project TREK): program feasibility and preliminary findings. J Pediatr Hematol Oncol. 2008 Apr;30(4):272-80. DOI: 10.1097/MPH.0b013e318162c476.
46. Cox CL, McLaughlin RA, Rai SN, Steen BD, Hudson MM. Adolescent survivors: a secondary analysis of a clinical trial targeting behavior change. Pediatr Blood Cancer. 2005 Aug;45(2):144-54. DOI: 10.1002/pbc.20389.
47. Hudson MM, Oeffinger KC, Jones K, Brinkman TM, Krull KR, Mulrooney DA, et al. Age-dependent changes in health status in the Childhood Cancer Survivor cohort. J Clin Oncol. 2015 Feb 10;33(5):479-91. DOI: 10.1200/JCO.2014.57.4863.
48. Li HC, Chung OK, Ho KY, Chiu SY, Lopez V. Effectiveness of an integrated adventure-based training and health education program in promoting regular physical activity among childhood cancer survivors. Psychooncology. 2013 Nov;22(11):2601-10. DOI: 10.1002/pon.3326.

49. Rabin C, Dunsiger S, Ness KK, Marcus BH. Internet-Based Physical Activity Intervention Targeting Young Adult Cancer Survivors. J Adolesc Young Adult Oncol. 2011 Dec;1(4):188-94. DOI: 10.1089/jayao.2011.0040.
50. Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. Exploring Mediators of Physical Activity in Young Adult Cancer Survivors: Evidence from a Randomized Trial of a Facebook-Based Physical Activity Intervention. J Adolesc Young Adult Oncol. 2015 Mar 1;4(1):26-33. DOI: 10.1089/jayao.2014.0034.
51. Sasso JP, Eves ND, Christensen JF, Koelwyn GJ, Scott J, Jones LW. A framework for prescription in exercise-oncology research. J Cachexia Sarcopenia Muscle. 2015 Jun;6(2):115-24. DOI: 10.1002/jcsm.12042.
52. Schnyder S, Handschin C. Skeletal muscle as an endocrine organ: PGC-1alpha, myokines and exercise. Bone. 2015 Nov;80:115-25. DOI: 10.1016/j.bone.2015.02.008.
53. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst. 2012 Jun 6;104(11):815-40. DOI: 10.1093/jnci/djs207.
54. Repka CP, Hayward R. Oxidative Stress and Fitness Changes in Cancer Patients following Exercise Training. Med Sci Sports Exerc. 2015 Nov 19. DOI: 10.1249/MSS.0000000000000821.
55. Tonorezos ES, Oeffinger KC. Survivorship after childhood, adolescent, and young adult cancer. Cancer J. 2008 Nov-Dec;14(6):388-95. DOI: 10.1097/PPO.0b013e31818f5aba.
56. Jones LW, Liang Y, Pituskin EN, Battaglini CL, Scott JM, Hornsby WE, et al. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. Oncologist. 2011;16(1):112-20. DOI: 10.1634/theoncologist.2010-0197.
57. Schneider CM, Hsieh CC, Sprod LK, Carter SD, Hayward R. Effects of supervised exercise training on cardiopulmonary function and fatigue in breast cancer survivors during and after treatment. Cancer. 2007 Aug 15;110(4):918-25. DOI: 10.1002/cncr.22862.
58. Bourke L, Homer KE, Thaha MA, Steed L, Rosario DJ, Robb KA, et al. Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. Br J Cancer. 2014 Feb 18;110(4):831-41. DOI: 10.1038/bjc.2013.750.
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 leukaemia - From the St. Jude Lifetime Cohort. Br J Haematol. 2014 May;165(3):364-74. DOI: 10.1111/bjh.12754.
60. Biswas SK. Metabolic Reprogramming of Immune Cells in Cancer Progression. Immunity. 2015 Sep 15;43(3):435-49. DOI: 10.1016/j.immuni.2015.09.001.