Sports Medicine
https://doi.org/10.1007/s40279-022-01759-z

REVIEW ARTICLE

Resistance Training for Patients with Cancer: A Conceptual Framework for Maximizing Strength, Power, Functional Mobility, and Body Composition to Optimize Health and Outcomes

Colin E. Champ[1,2,3,6] · **David J. Carpenter**[1,3] · **Alexander K. Diaz**[1,3] · **Jared Rosenberg**[3,4] · **Bradley G. Ackerson**[1,3] · **Parker N. Hyde**[3,5]

Accepted: 18 August 2022

Abstract

There are many benefits to the addition of exercise to cancer treatment and survivorship, particularly with resistance training regimens that target hypertrophy, bone mineral density, strength, functional mobility, and body composition. These goals are best achieved through a series of individualized high-intensity compound movements that mirror functional mobility patterns and sufficiently stress the musculoskeletal system. As a result of adequate stress, the body will engage compensatory cellular mechanisms that improve the structural integrity of bones and muscles, stimulate metabolism and the immune system, optimize functional performance, and minimize mechanical injury risk. The current evidence suggests that application of the above exercise principles, practiced in a safe environment under expert observation, may offer patients with cancer an effective means of improving overall health and cancer-specific outcomes. The following article poses several important questions certified exercise specialists and physicians should consider when prescribing resistance exercise for patients with cancer.

Key Points

Exercise, and specifically resistance training, is becoming more commonly a part of cancer care owing to the array of benefits it provides.

Resistance training regimens that target hypertrophy, bone mineral density, strength, functional mobility, and body composition may improve outcomes and quality of life for patients with cancer.

Methods to optimize these metrics should be individualized and intense exercise regimens that adequately stress the musculoskeletal system should be implemented and observed by qualified personnel.

1 Introduction

Sarcopenia, obesity, strength, and functional mobility deficits present significant challenges to patients with cancer both during and after cancer treatment. Sarcopenia and

---

✉ Colin E. Champ
Colin.Champ@Duke.edu

[1] Department of Radiation Oncology, Duke University Medical Center, 20 Duke Medicine Circle, Durham, NC 27710, USA

[2] Department of Radiation Oncology and Exercise Oncology and Resiliency Center, Allegheny Health Network, Pittsburgh, PA, USA

[3] Exercise Oncology and Resilience Group, Pittsburgh, PA, USA

[4] Department of Exercise Science, Syracuse University, Syracuse, NY, USA

[5] Department of Kinesiology, University of North Georgia, Dahlonega, GA, USA

[6] Inspire Oncology, Exercise Medicine, Naples, FL, USA

obesity are associated with an increased risk of cardiovascular disease in cancer survivors [1]. Furthermore, the impaired physical fitness, frailty, and decreased bone health that accompany many treatment strategies place patients with cancer at a higher risk for falls, fractures, hospitalizations, and mortality [2]. Patients with cancer experience high rates of orthopedic issues such as pain, neuropathy, limited mobility, and frailty [3, 4], as well as musculoskeletal issues such as sarcopenia, decreased muscle mass and strength, and decreased bone mineral density (BMD) [5]. These issues are also related to survival outcomes, with reductions in muscle mass as well as various thresholds for "low muscle mass" associated with worse clinical outcomes after cancer treatment [6]. Additionally, sarcopenia, which is defined as the loss of skeletal muscle mass in addition to the loss of strength and/or reduced physical performance, is associated with decreased survival and increased toxicity from cancer treatments such as radiation therapy and chemotherapy [7].

Despite multiple studies demonstrating improved quality of life, physical function, and overall outcomes [8], exercise regimens and resistance training (RT) are still not a routine part of cancer treatment. To date, exercise oncology efforts have been inconsistent with general strength and conditioning principles, with many not reporting intensity, others utilizing fitness capacity tests for weight selection, and a large number failing to surpass adequate intensity to achieve RT goals [9]. Others have focused on aerobic training and high-repetition RT [10]. This may be partially responsible for the findings that in patients with cancer undergoing RT, improvements in body composition, i.e., increased lean muscle mass and decreased adipose tissue, have not paralleled those seen in healthy populations undergoing similar training [11].

While specific protocols aimed at improving strength and hypertrophy have been established in the literature, the majority are hesitant to apply contemporary RT and performance principles that would typically be utilized in individuals without cancer, including linear and undulating periodization, compound movements, and progression, partially owing to fear of exacerbating conditions such as lymphedema [9, 12, 13]. The latter has been disproven, as weight training has been found to be safe with a minimal risk of exacerbating or promoting lymphedema [14]. While some studies have included aerobic exercise as a form of periodization, the implementation of other principles occurs less frequently [13, 15]. Additionally, current wearable and technological advances (e.g., heart rate variability) have dramatically improved the ability of the exercise and medical professionals to not just qualitatively assess patient recovery, but to also make quantitative data-driven decisions on training volume/load/intensity in the program [16, 17]. Such feedback can allow the prescribing exercise specialist to modify load and intensity on days when underperformance is expected. Last, sports performance strategies such as cluster sets and other methods to increase load and volume can help to maximize the benefits of RT [18]. After accounting for any individual-specific deficits, it is unclear whether these principles should vary from general hypertrophy and performance recommendations, with current data suggesting similar approaches should be based on the overall goals of training [19].

While RT efforts have increased over the past several years, implementation of exercise principles has progressed slowly within cancer populations because of safety concerns [20]. As a result of cautiousness and the need to establish safety and validity, these aforementioned regimens have generally focused on open-chain exercises and machine-based lifts that isolate muscles often in seated positions, as opposed to compound body movements and free weight exercises to improve strength, mobility, function, and hypertrophy [9]. As exercise prescriptions become more advanced and relevant to patients with cancer, newer regimens should mirror exercise principles used in noncancer populations while accounting for the health of each individual and specific limitations relating to their diagnosis and treatment [19]. The ability to allocate individuals either under treatment or previously treated for cancer to groups of varying needs based on their physical status and type of cancer treatment, which range from rehabilitation and general physical therapy to an introduction to RT and advanced training, the optimization of strength, performance, and body composition is particularly important owing to the large array of treatments and residual treatment-related effects that will impact training regimens. For instance, the treatment of advanced or aggressive breast and prostate cancer may include chemotherapeutic regimens and androgen deprivation therapy that result in significant deconditioning, fatigue, loss of muscle and strength, and peripheral neuropathy [21–23]. This must be strongly considered in the exercise regimen and approach.

However, the treatment of early-stage breast and prostate cancer, including only surgery and/or radiation therapy and hormone therapy, generally leaves individuals with minimal deficits and at an exercise capacity similar to that of the general population [24]. In the breast cancer population, reported adherence to RT in research protocols is excellent and on average 84% [24]. Thus, vital movement patterns of push, pull, core, squat, and hip hinge can be targeted in RT regimens to optimize body composition, strength, and mobility utilizing established RT principles such as periodization and progression, specificity, and overload.

While many of the early RT programs in exercise oncology have followed these essential underpinnings (specificity: 100% of studies, progression: 65% of studies and overload: 76% of studies) of a RT program and per American College of Sports Medicine guidelines, almost 50% have employed the nearly *identical* program designs [13]. This clearly

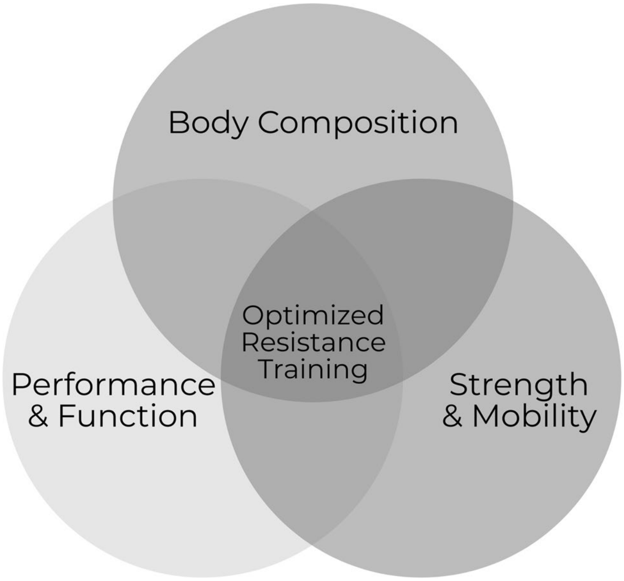

Fig. 1 Overlapping goals of resistance training in the oncology setting

demonstrates a need for contemporary RT programs for cancer populations to expand beyond methodologies used to establish initial safety and efficacy objectives, instead of addressing the dramatic need to begin to treat exercise as medicine and provide *targeted RT 'therapy.'*

When the dichotomous examples proposed above are observed in both clinical and exercise facilities, it has become evident that there is no 'one-size-fits-all' program that can be applied to RT and cancer. Instead, certified exercise specialists and physicians must together consider many guiding principles including individualization of patient goals, both ongoing and potential therapeutic side effects, competing comorbidities, and motivational status. One such example of targeted RT is demonstrated by Fairman et al., who proposed the use of 'auto-regulation' strategies that allow for qualitative and potentially quantitative approaches heart rate variability (HRV) to guide the factors affecting exercise quality (volume, time, and load/intensity) [17].

This article proposes key areas for consideration of RT regimens, program design, and specific outcome factors targeted to patients with cancer to guide the increasing utilization of exercise therapy as a foundational component of routine cancer care. While optimal repetition and RT approaches are addressed elsewhere [25], the following are questions certified exercise specialists and physicians should consider when prescribing RT for patients with cancer in order to target the maximal number of modifiable areas and optimize the likelihood and magnitude of corresponding patient-specific benefits (Fig. 1).

2 Body Composition: Hypertrophy, BMD, and Adiposity

2.1 Is the Exercise Regimen Sufficient to Improve Hypertrophy and Body Composition?

Muscle mass loss of up to 50% is common with aging owing to atrophy of type II muscle fibers and a decrease in the overall number of muscle fibers. This correlates with losses in strength and mobility and a higher risk of falls [26]. Rates of muscle loss and sarcopenia appear to be higher among patients with cancer than the general population [5], and skeletal muscle depletion is independently predictive of unfavorable clinical outcomes across a range of cancer histologies [6]. A recent analysis of body composition via a computed tomography scan assessment in 3241 women treated for breast cancer revealed an independent correlation of both sarcopenia and high amounts of adipose tissue with higher mortality rates. These associations outperformed BMI as a marker of mortality, illustrating the prognostic significance of adequate muscle mass even in the presence of lower adipose tissue [27]. Adequate muscle mass provides an array of benefits, including enhanced strength and physical function, a reduced risk of falls and fractures, and enhanced metabolic function and insulin sensitivity [28–30].

While hypertrophy is vital for patients with cancer, optimization of muscle fiber type via the exercise regimen is important as well. Aging and an over-reliance on aerobic training can reduce the ratio of type II fast-twitch to type I muscle fibers [31, 32]. Type II muscle fibers are primary affected via high-load resistance and hypertrophy training, as these fiber types provide muscles the mechanical ability to rapidly develop force and power [33, 34]. Cachexia, a multifaceted syndrome of profound muscle and weight loss accompanied by systemic inflammation and metabolic dysfunction, may account for up to 20% of cancer-related deaths, further illustrating the importance of muscle mass preservation [35]. Recent work has revealed that RT can improve muscle mass in cachectic individuals with pancreatic cancer [36]. Additionally, the contracting muscle secretes anti-inflammatory hormones such as muscle-derived interleukin-6, which may further benefit patients with cancer after treatment [37].

The most potent method to increase muscle mass is through hypertrophy promoted by RT. Skeletal muscle myocytes are post-mitotic, meaning minimal cell replacement is possible within muscle cells. As such, muscle fiber repair and restoration are vital to maintain or increase muscle mass [38]. Myogenic stem cells remain quiescent within the sarcolemma and basal lamina of muscle fibers, and are activated via mechanical stimuli that produce microtrauma, the subsequent release of growth factors, and the influx of immune cells including macrophages and neutrophils, ultimately promoting the migration and fusion of these satellite cells to aid in repair and restoration [39]. The exact mechanism by which hypertrophy occurs remains unclear and is likely multifactorial, but it appears that the ability of these satellite cells to donate nuclei to myofibrils supports the ability of the muscle fiber to synthesize contractile proteins and increase both cross-sectional area and number of myofibers [40]. Migration of these satellite cells occurs after even a single bout of intense exercise [41]. Additionally, the Akt/mammalian target of rapamycin pathway is the cellular regulator of hypertrophy; muscle overload promotes activation of mammalian target of rapamycin and subsequent muscle protein synthesis and hypertrophy [42]. Overloading muscle tissue results in the release of muscle-specific interleukin-6, which promotes satellite cell proliferation and migration and hypertrophy via a paracrine mechanism [43].

An array of structural, hormonal, and metabolic changes during exercise appears to largely influence hypertrophy. Generally, according to Schoenfeld, three primary factors promote muscle hypertrophy during RT [38]:

1. Mechanical tension.
2. Muscle damage.
3. Metabolic stress.

Additionally, rates of protein synthesis within muscle tissues must be greater than protein degradation, the former being stimulated by tension upon the muscle, chronic overloading of the muscle, and periodic strain of the muscle tissue [44]. Dietary protein and amino acids facilitate protein synthesis and muscle anabolism 24–48 h after a bout of exercise; however, the initiating stimulatory signal via RT is required to elicit any changes [45]. This signal includes mechanical overload to the muscle via progressive tension and loads producing microtrauma to the muscle tissue and resultant neutrophil immune cell influx, growth factor release, and satellite cell activation, proliferation, and differentiation [39]. In other words, skeletal muscle acts as a mechanosensitive cell type, and a mechanical stimulus must be large enough to elicit an adaptive physiologic response (Fig. 2) [44].

Overloading the muscle appears to promote adaptation and hypertrophy at all ages, including individuals older than 90 years of age experiencing significant hypertrophy after an intensive overload of muscle tissue [46]. Hypertrophy after muscle overload is similarly independent of biological sex. While the exact mechanisms that promote hypertrophy remain less clear, the requirement of an initial and repetitive amount of sufficient force and muscular overload to promote an adaptive response is well defined. Exact repetition schemes and workout regimens to elicit hypertrophy remain unclear, with the caveat that several general principles for eliciting maximal hypertrophy are supported by considerable research.

Multiset protocols, in the absence of overtraining, appear to provide a larger stimulus for hypertrophy than single sets, especially when training the lower body [38, 47]. While studies vary, performing at least 4–6 sets per muscle group may be required to achieve a baseline of hypertrophy. A recent analysis demonstrated that set number is proportional to muscle hypertrophy, with 5–9 sets per muscle per week producing greater hypertrophy than under 5 per week, and 10 or more sets/week providing the greatest amount of hypertrophy. Additional sets may be required in experienced lifters [48].

Studies comparing hypertrophy rates following low-intensity ($\leq 50\%$ one-repetition maximum [RM]) versus high-intensity ($\geq 60\%$ 1RM) RT have shown mixed findings [47]. In untrained individuals, initial low-load training can stimulate significant hypertrophy. However, this effect becomes less clear in trained individuals experiencing hypertrophic adaptation.

In addition to noted benefits in maximal strength and power, training at higher loads and a higher %1RM ($> 80\%$) appears to maximally benefit BMD, as discussed below in Sect. 2.2. Thus, while hypertrophy can be reached at both high and low training in the novice, more intense (i.e., higher load) training may provide a larger spectrum of beneficial changes for patients with cancer [49].

2.2 Body Composition: BMD

Muscles serve as the primary driver of functional mobility, strength, and metabolic health, while the skeletal system serves as the major structural component of the human body. Bone mineral density, which can be accessed via the quantification of image-based optical bone density, serves as a reliable surrogate for fracture risk. While BMD generally decreases during adulthood at an initial rate of approximately 0.5% per year [26], many patients with cancer experience an acceleration of this decline via cancer-specific treatments such as anti-estrogen and anti-androgen agents [21]. Gastrointestinal cancers can lead to nutritional deficiencies such as vitamin D deficiency and subsequent secondary hyperparathyroidism that greatly decrease BMD and accelerate osteoporosis in both men and women [50]. Resultant increases in fracture risk are significant in the context of baseline fall and fracture prevalence rates of 30% in free-living individuals over the age of 65 years and 50% of individuals in care facilities and nursing homes. Moreover, fractures in individuals with osteoarthritis (i.e., low BMD) are associated with higher rates of mortality [51]. While the methods described above to improve strength, power, gait,

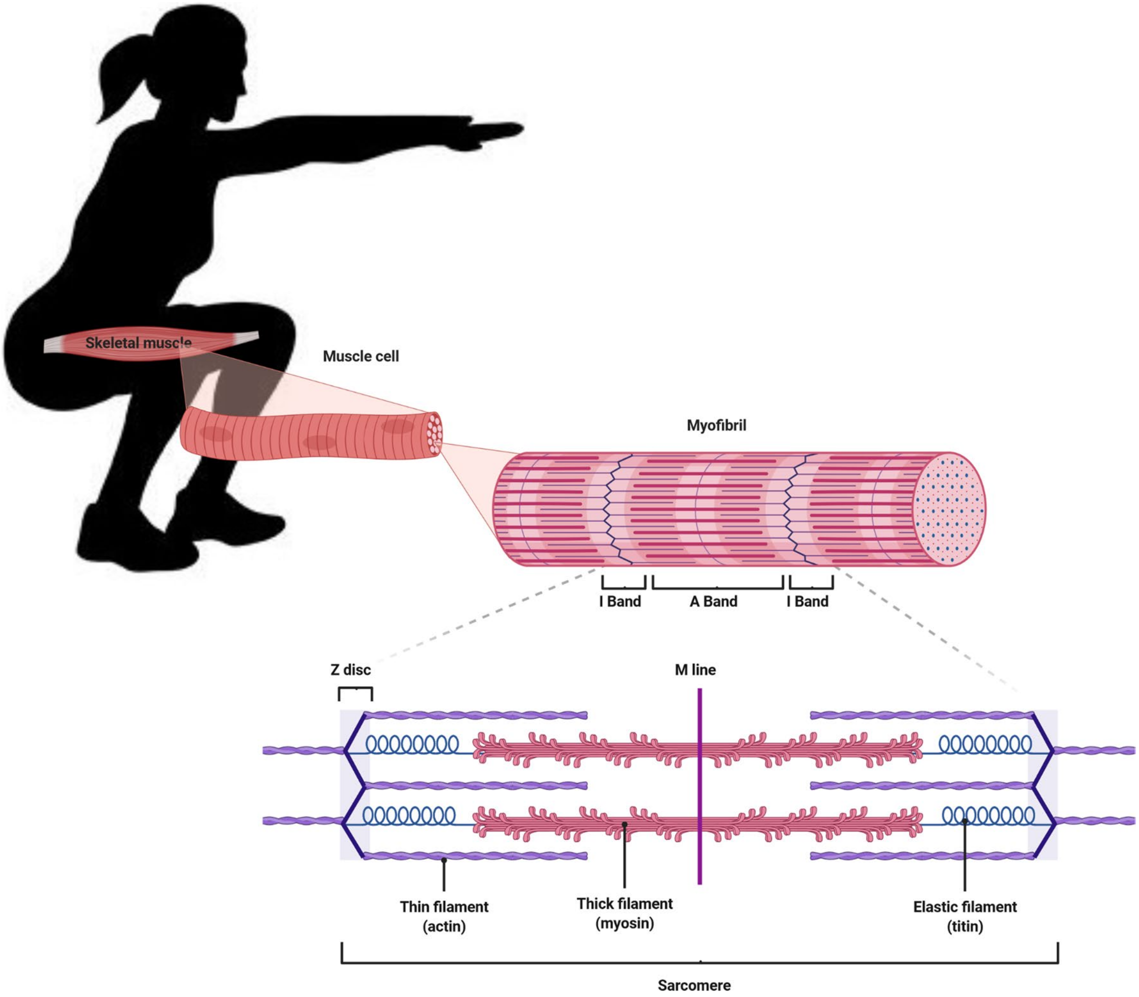

Fig. 2 Squat exercise provides substantial mechanical stimulus to the quadriceps muscle and sarcomere

proprioception, and mobility will reduce the risk of falls, BMD presents an additional modifiable risk factor through which RT may further reduce fracture risk in patients with cancer.

The bone acts as a mechanostat while providing structural support to the body, transmitting mechanical signals to the cellular processes that promote increases in bone mass and density. Adaptive increases in bone structure and density serve as a protective measure to offset further and habitual mechanical stresses and deformation that could threaten bone integrity [52]. Much as is the case with muscular hypertrophy, a sufficient force must be applied to the bone to promote new bone formation. This threshold, known as the minimal essential strain, is the point when new bone formation is stimulated, and is generally felt to be approximately 10% of the force required to result in bone fracture [53, 54].

According to Turner, three major rules generally govern the ability of exercise to stimulate bone growth: [55]

1. It is driven by dynamic, rather than static, loading.
2. Only a short duration of mechanical loading is necessary to initiate an adaptive response.
3. Bone cells accommodate to a customary mechanical loading environment, making them less responsive to routine loading signals.

This latter relationship provides insight into the optimal mechanisms to improve BMD through exercise regimens that provide compression, tension, and shear stresses to the bones. Progressive overload, i.e., providing progressively greater mechanical demand on the bones through specific exercises utilizing low repetition numbers and loads within each workout, is most effective at eliciting a compensatory response that promotes increased BMD [56]. Additionally, habitual stress and bony deformation is required, with studies revealing a requisite of at least 6 months of RT to promote an adaptive response leading to improved BMD.

Among the necessary components for stimulating BMD improvement, targeting the aforementioned minimal essential strain appears vital to exercise design. For instance,

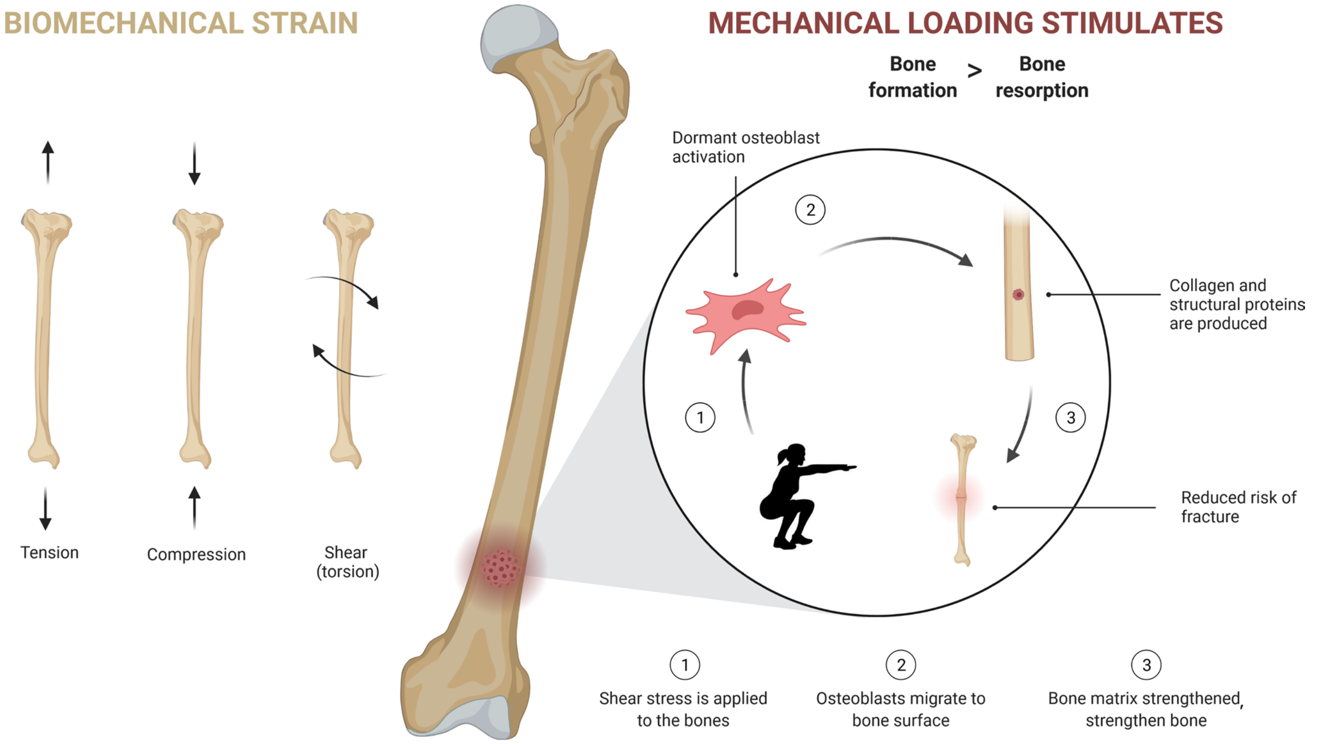

Fig. 3 Adequate biomechanical strain and mechanical loading promotes cellular and mechanical mechanisms to strengthen the bones

BMD improvements were not observed in women undergoing 24 weeks of circuit training and strength training at 45–80% 1RM of 2–4 sets of 6–20 repetitions of lower extremity machine exercises and upper body machine and free-weight exercises, though strength and cardiorespiratory fitness were improved [57]. The threshold for eliciting osteoblast migration and bone formation and halting bone resorption was likely not met by mechanical strain associated with 45–80% 1RM [58]. Conversely, significant increases in lumbar spine and femoral neck bone mineral content were observed in postmenopausal women with osteoporosis or osteopenia following a 12-week regimen of 4 sets of 3–5 repetitions of squats at 85–90% of 1RM, with concordant increases in 1RM strength and the rate of force development [59].

In addition to targeting higher 1RM percentages (i.e., high-intensity), BMD improvements may be further stimulated through judicious selection of compound exercise movements. Compound exercises tend to apply multiple directional forces and mechanical stresses to the bones, including tension, compression, and shear stress (Fig. 3). In a prospective trial of 101 postmenopausal women, randomization to a twice-weekly high-intensity impact training regimen utilizing compound movements including the deadlift, overhead press, and back squat for 5 sets of 5 repetitions with an intensity of > 80–85% 1 RM followed with jumping chin-ups with drop landings promoted significant increases in BMD, particularly in the lumbar spine, versus home-based low-intensity exercise [60]. Additionally, femoral neck cortical thickness, which is closely correlated with hip fracture, was increased [61]. Concerns that high-intensity compound movements may place postmenopausal women at increased risk for exercise-induced injury appear unfounded, as no related adverse events were observed in this trial.

Data reveal a positive linear relationship between exercise load and BMD [62]. The response of bone to maximal peak loading appears to be site specific based on the mechanical stress produced via each specific workout, promoting exercise patterns and movements that load multiple bones and joints, providing shear stress to produce global improvements in BMD [63]. Accordingly, power training has been shown to offset BMD loss in postmenopausal women [64]. As lean body mass has been shown to be the main determinant in peak BMD, exercise regimens that can increase hypertrophy would be expected to positively affect BMD [65]. In a cohort of young female athletes, habitual high-impact exercise with forces three to six times body weight has revealed higher BMD and bone formation versus medium-impact and low-impact activities [66]. Similar findings in female athletes aged 42–50 years reveal increased BMD following high-impact exercise [67]. These effects appear to be less pronounced in the postmenopausal population, though it is unclear if this is an artifact of less intense regimens tested in these individuals or delayed changes in BMD [57, 63].

These methods have carried over into the oncology literature, as multiple studies have revealed that impact training and RT can offset BMD loss in the setting of androgen deprivation therapy [68, 69]. Additionally, patients with menopausal breast cancer experienced slowed BMD loss in the spine with impact training and RT [70]. While increases in BMD were not seen, these regimens generally used 6–12 repetitions per exercise, and it is thus unclear if RT is able to increase BMD in these individuals with the usage of higher loads. They did employ impact training such as jumps and lands; this finding combined with the results helps readers to assume that the bones and joints received sufficient loading. Further data are needed to demonstrate whether greater loading will result in a more beneficial response and possibly improve/increase BMD over time.

Exercise methods vary widely across studies. Accordingly, the significance of serial BMD measurements before and after exercise may be difficult to discern where exercise methods appear insufficient for eliciting osteocyte migration, calcium deposition, and resultant BMD increases. There may be concern that RT in the cancer population could cause more harm than good. Supervision by trained personnel is highly recommended to ensure that exercise intensity is sufficient for stimulating BMD changes while maximizing safety. The aforementioned evidence shows that correct RT protocol implementation within cancer populations provides significant benefits with minimal injury risk.

In summary, the above data suggest that patients with cancer may achieve optimal BMD improvements by utilizing high loads, lower repetitions, and movements that require rapid production of force through dynamic movements providing shear stress to multiple bones and joints. Exercises should prioritize loading of the spine and hips, as these locations are at the highest risk for fractures. General principles of BMD preservation and improvement are vital for patients at risk of accelerated BMD degradation from cancer-specific treatments.

2.3 Body Composition: Adiposity

Adipose tissue refers to a connective tissue made up of adipocytes, fibroblasts, blood, immune cells, and nervous tissue. It has various physiological roles depending on its classification as white adipose tissue or brown adipose tissue. White adipose tissue primarily stores energy as triglycerides, thermally insulates, and provides protection [71]. Ingestion of any of the three macronutrients can ultimately lead to weight gain and obesity through proliferation of white adipose tissue. In the human body, adiposity is mainly located subcutaneously and around internal organs. There is high variability among individuals in the body volume composed of adipose tissue, with a range from < 7% in elite athletes to > 50% in obese individuals [72]. These normal ranges differ significantly between age groups, sexes, and activity levels. Waist circumference, waist-to-hip ratio, and dual-energy X-ray absorptiometry are common methods of determining a person’s volume of body fat. Body mass index is a validated and widely used index that uses height and overall weight to inform patients of their risk for disease and mortality [73]. This importantly does not incorporate measures of adiposity or distribution of weight in its calculation and risk stratification.

Decreases in body fat percentage are mediated through a bioenergetic state whereby overall calories expended exceed calories consumed. Resistance training-based exercise regimens are capable of yielding such a deficit by two interrelated mechanisms: increased metabolic expenditure via direct caloric expenditure and excess post-exercise oxygen consumption, as described below in Sect. 4.1, and maintenance/hypertrophy of increased muscle mass leading to increases in the basal metabolic rate. The Katch–McArdle formula uses lean body mass, or weight and body fat percentage to calculate the basal metabolic rate or resting daily energy expenditure [74]. It shows a direct relationship between increased lean body mass and basal metabolic rate. Multiple studies including a large meta-analysis have suggested that there is equal benefit to aerobic training programs and RT programs for the goal of decreasing adipose tissue and percent body fat [75].

Minimizing excess adipose tissue is particularly relevant to patients with cancer. Obesity is estimated to cause approximately 20–27% of all cancer cases [76], and it is linked to increased rates of complications and side effects from systemic therapies, surgery, and radiation therapy [77]. A recent meta-analysis of over 6 million patients across 203 studies found that obesity was associated with increased mortality across most cancer types [78]. In the context of breast and prostate cancer, widely used hormonal treatments put patients at greater risk for abdominal obesity, hyperglycemia, and hypertriglyceridemia, thereby increasing cardiovascular mortality risk [79]. Adiposity is directly associated with a risk of developing cancer, the ability to undergo and respond to related therapies, and associated survival outcomes. A recent analysis of 58 studies reveals the ability of RT to reduce overall and visceral adipose tissue [80].

The American Society of Clinical Oncology’s Position Statement on Obesity and Cancer recommends consultation with “an exercise therapist or trainer or physical exercise classes,” noting these services are not covered by Medicare and rarely by Medicaid or private insurance [81]. These guidelines do not address exercise methodology. Regarding cancer-related obesity, meta-analyses have revealed reductions in adipose tissue along with increases in muscle mass from RT [11]. Thus, we recommend high-intensity RT that targets hypertrophy through compound movements as previously described to stimulate the basal metabolic rate via increased lean body mass. Patients with cancer may derive significant benefit from an optimal balance of adipose tissue and lean body mass across all stages of care.

3 Strength, Power, Balance, Mobility, and Proprioception

3.1 Does the Regimen Improve the Fundamental Movement Patterns?

Across aging populations, declining motor performance leads to increased prevalence of associated injuries, resulting in falls and increased hospitalizations. Increases in comorbid conditions such as obesity and type 2 diabetes mellitus further compound this decline [82]. The morbidity and mortality that accompanies falls can be extensive; 95% of hip fractures result from mechanical falls with a 12-month fatality rate of 20% [51]. Additionally, proprioception worsens with age, particularly in the lower extremities, directly impacting posture, balance, and gait [83]. Resistance training is an effective method for improving strength, power, balance, mobility, proprioception, and corresponding general physical and motor performance, providing a reduced risk of falls and increased ability to engage in future dynamic exercises. Optimizing physical and motor performance may be particularly beneficial to patients with cancer, who are often at an increased risk of fracture and other impairments secondary to their diagnosis and treatment [2]. The following section will discuss several aspects of motor performance and functional mobility that the oncologist should consider when prescribing or referring patients for exercise therapy.

3.2 Functional Movement

Exercise is the most direct method to increase physical functioning and performance, specifically through exercise routines that utilize and improve muscular fitness and fundamental movement patterns (push, pull, hinge, squat, and core activation). Specificity of workouts is vital, as regimens should be aimed at targeting and improving task-specific activities, focusing on exercises that specifically imitate and improve typical movement patterns. A large proportion of fractures occur because of a loss of strength and balance issues [56]. Optimal functional movement ability improves balance, proprioception, gait, and dynamic agility, and is directly associated with a lower risk of injury, particularly among the elderly [84, 85]. Compound and functional movements with opposing resistance are performed with the goal of improving and optimizing particular movements or activities, specifically those of activities of daily living, which can help prevent falls and injury [86]. Compound exercises employing functional movements rely on coordination, balance, and extensive muscular activation to offset shear stresses during joint movement. For instance, closed-chain lower body exercises such as squats and lunges significantly load the tibiofemoral and patellofemoral joints, relying on exquisite control of these joints and muscles to maintain control and balance to avoid falls and injury [87]. An array of studies reveal the advantages over closed-chain versus open-chain exercises to reduce the risk of falls and improve static and dynamic balance [88, 89]. However, it should be noted that to date, there is limited evidence addressing the effects of exercise on activities of daily living performance in patients with cancer as few studies have evaluated the effects of exercise on physical disability measures, and those that exist reveal small changes. Further research in this area is warranted [90].

In addition to compound movements and heavy weight resistance, the inclusion of exercises involving all planes of motion (coronal, sagittal, and axial) and all basic movement patterns (push, pull, hinge, squat, lunge, and carry/walk) may further optimize functional mobility, athletic ability, and physical performance. Exercise selection should improve participants' daily activities, with a range from non-impactful activities such as walking to preventing falls and injuries during sporting activities such as tennis, golf, or other more intense activities. The addition of functional training with vertical and horizontal movement components, object carrying, and floor work has been shown to improve activities of daily living assessment compared with RT alone [91]. Compound lifts, like the deadlift and squat, require trunk activation and enhance core stability [92]. Compared to stationary machine exercises, free-weight exercises rely on additional activation of the stabilizers, plantar and knee flexors, and enhanced quadriceps and knee extensor activation to enhance gait speed [93]. Biomechanical studies reveal that squatting, whether traditional, goblet squat, or box squat, provides an array of shear stresses and linear displacement on the long bones and joints through varying moment arms at the hips, knees, ankles, and lumbosacral spine (Fig. 3) requiring intense coordination and core activation for stability [94].

Regimens utilizing heavier weights and repetition schemes with higher 1RM percentages per set activate large muscle fibers, thus providing enhanced strength and hypertrophy gains [25]. Unilateral and bilateral strength training have demonstrated similar improvements in hypertrophy and muscle activation in untrained women, while unilateral training improved unilateral activation and strength gains that may be more beneficial in the setting of imbalance and avoiding falls [95]. To ensure safety, exercise regimens including compound movements and heavy intense lifts should progress from large to small muscle groups and from compound movement patterns to isolated exercises throughout the workout. Performance can become impaired toward the end of workouts because of physical and neurological fatigue, thus favoring early use of multi-joint synergistic, large muscle, and intense workouts to optimize performance and control [25].

More intense regimens utilizing heavier weights and greater loads lifted may provide the largest benefits for patients when applied in a safe and monitored setting. For instance, heavy lifting and load increases at 80% 1RM in 63-year-old women and 87-year-old men increased their speed, strength, power, and muscle mass [96]. Across intense regimens, the addition of explosive training and plyometrics increases trunk muscle activation and hip and thigh power versus static lifts alone [92, 97, 98]. Exercises that utilize these principles will enhance the fundamental movement patterns of patients with cancer to improve strength, balance, mobility, and proprioception.

3.3 Strength and Power

Meta-analyses in non-cancer populations have demonstrated greater improvements in lower-limb strength following higher intensity and progressive RT than moderate-intensity and low-intensity regimens [99]. Exercise regimens that progressively overload the muscles will promote greater muscle and cross-sectional area recruitment, muscle fiber discharge, enhanced neural function, and maximal improvements in strength [100]. Notably, while strength gains are greater in novices and untrained individuals than well-trained or intermediate individuals, the same general principles hold for maximizing strength, albeit greater loads are required as individuals progress [25].

Improvements in strength will enhance motor control and performance and reduce the risk of injury, especially in older individuals. Gains in strength led to improvements in gait speed and functional mobility in elderly men undergoing intense RT, with some participants up to 96 years of age [101]. In a second study of elderly men with an average age of 84 years, completion of a similar 10-week RT protocol showed significantly greater improvements in knee extensor muscle strength and endurance, 6-min walk test, stair-climbing power, and chair-rising time. This intense RT protocol included 3 sets of 8 repetitions, three times per week for 10 weeks at 80% 1RM, and was compared to a training protocol at low intensity (40% 1RM) [102]. These changes in strength were significantly related to the changes in functional outcomes, reinforcing the association between motor performance and functional mobility in this population. Total body exercises that require rapid force production and an interplay of multiple joints and muscles (power cleans, clean and press, jumps) can largely impact power production, improving overall performance and motor function at any level of expertise [103].

In summary, exercise regimens that contain a majority of exercises involving free weights and compound movements that utilize movement-based exercises will maximally increase athletic ability, proprioception, stability, motor function, and performance. These include a mixture of bilateral and unilateral exercises that engage fundamental movement patterns. Stationary, open-chain, and machine-based exercises should be limited or intermixed, as they may not provide as broad a range of benefits.

4 Metabolism and Immune Function

4.1 Does the Exercise Regimen Positively Impact the Immune System and Metabolism?

Physical activity has been shown to have both inhibitory and stimulatory effects on the immune system, depending on length and intensity, thereby modulating the risk of infection [104]. Infection risk versus exercise workload reveals a “J”-shaped curve, with infection risk dropping significantly from moderate exercise and rising with excessive exercise [105]. Exercise length and intensity are known to suppress T-cell and B-cell function and natural killer cell activity, which may increase the risk of infection [104]. For instance, a seminal report of 1901 Boston Marathon runners demonstrated pronounced leukocytosis that resembled an inflammatory response [106]. While prolonged exercise can promote excessive production of catecholamines, stress hormones, and inflammatory cytokines that negatively impact immune function, these findings are not reproduced following acute bouts of exercise lasting 60 min or less [107]. Furthermore, acute exercise regimens have been shown to enhance immunosurveillance against cancer cells and reduce systemic inflammation by activation and immobilization of neutrophils, natural killer cells, and CD8 + T lymphocytes [108]. Additionally, transient increases in muscle-derived interleukin-6 are observed following acute exercise regimens, promoting lipid and glucose metabolism and lowering chronic inflammation [37].

While intense progressive RT utilizing repetitions at 80% 1RM do not appear to promote an increase in cytokines or inflammatory factors, the immunomodulatory significance of high-intensity RT remains poorly defined [109]. A secondary analysis of several year-long randomized controlled trials comparing resistance exercise to placebo in breast cancer survivors revealed decreased C-reactive protein levels following exercise [110]. Interestingly, this change was only seen in women who increased their strength throughout the RT regimen, highlighting the need for dynamic RT regimens that target mechanical and structural physiological changes.

Resistance training promotes acute leukocytosis via varying mechanisms, including muscular tissue trauma and damage, shear stress, and hormonal signaling. After an acute session of RT, increases in circulating levels of neutrophils, natural killer cells, and monocytes aid in muscle repair and growth [111]. This effect varies based on age, sex, and exercise specifics, and generally appears to be more of an acute phenomenon, with chronic exercise showing little change in circulating leukocyte counts.

While the exact impact of exercise on immune function remains unclear, the impact of exercise on metabolism and resting metabolic rate is more elucidated. In addition to the direct usage of energy and metabolites during the exercise regimen, differing regimens provide downstream metabolic effects.

Resting metabolic rate is responsible for the majority of total daily energy expenditure, and is proportional to muscle mass and fat-free mass [112]. Daily energy expenditure via physical activity has steadily declined and resting metabolic rate now accounts for over half of the daily energy expended in Western societies [113]. Attempts to account for this drop via vigorous exercise are largely ineffective because of the required amount to offset such a deficit [114].

Resting metabolic rate drops until around age 20 years, then plateaus until around age 60 years, at which point energy expenditure declines [112]. This decline is directly related to loss of lean mass, among other factors that accompany aging. Thus, increasing lean mass and therefore the resting metabolic rate through exercise may improve metabolic function and decrease adipose tissue, further supporting the rationale for targeting hypertrophy in this population. Excess post-exercise oxygen consumption is greater following high-intensity anaerobic training than aerobic training, demonstrating a greater metabolic stimulus related to replenishing fuel stores, hormone production, cellular repair, and anabolism [115, 116]. Short and intense exercises and movements can produce excess post-exercise oxygen consumption that accounts for up to 90% of the energy expended by the exercise [117]. Significant anaerobic metabolism products produced during heavy RT may account for part of the excess post-exercise oxygen consumption [118].

In addition to the metabolic benefits above, limiting exercise duration to ≤ 60 min is prudent for high-intensity exercise regimens targeting BMD and hypertrophy through compound movements due to considerable exertion and neuronal fatigue. Shortening rest time between sets, especially when segueing to open-chain or isolated exercises during the latter part of workouts, can increase the heart rate and produce a workout that achieves the immunomodulatory and metabolic benefits of acute exercise while avoiding potential inflammation.

5 Safety and Screening: Is the RT Regimen Safe for Patients with Cancer?

Prior to initiation of any RT regimen or exercise in general, patients with cancer should be cleared by the treating physician and assessed for unique physical limitations due to surgery, systemic therapy, radiation therapy, or other medical conditions. Nutritional status, symptoms burden, physical performance, and comorbid conditions must be assessed [119]. Additionally, as body composition and the above-mentioned metrics are vital in cancer populations, methods to assess these (bioimpedance analysis, dual-energy X-ray absorptiometry, ultrasound) should be part of the program. Beyond this screening process, the generation of customized workouts for the individual should mimic techniques utilized for RT approaches for the general population. Unfortunately, appropriate screening tests specific to RT and associated exercise selection are limited. When performed by experienced examiners, the Functional Mobility Screen (FMS) provides a baseline assessment to aid in the safe prescription of specific exercises, especially those relying on compound and functional movements [120]. Additionally, the FMS has been shown to significantly predict which individuals are at higher risk of injury with certain movement patterns [120]. Identification of specific mobility deficits may guide specific exercise prescription and optimize safety. These movement patterns can then be modified, assisted, or avoided based on the mobility limitation. The FMS can help expose which individuals require physical therapy assessment and prescription to enhance safety and mobility prior to initiating an exercise regimen.

The FMS can be utilized to identify individuals who rely on compensatory movement patterns during basic exercise movement patterns [121]. When subtle, such compensation can guide exercise avoidance and adaptation to minimize injury. When severe, corrective strategies can be applied or the individual may require a referral to physical therapy. The FMS is a pre-participation screening tool comprising seven movements, each scored from 0 to 3 [122]. A score of 0 is given if the participant experiences pain during the movement. One is given if the movement cannot be performed. Two is given if the movement is performed, but with compensatory movement observed, and three is given if the movement is performed correctly as instructed. It has been suggested that compensation in a movement may potentially predispose an individual to an injury [122]. Thus, the practitioner may use the FMS to individualize exercise selection by highlighting areas in need of improvement, as well as movement patterns without restrictions.

Other commonly utilized assessments include the 6-min walk and step test. Although these tests provide a useful context for cardiorespiratory fitness and general physical fitness, they should not be used to guide exercise selection and safety [123]. The get-up-and-go and sit-to-stand tests provide further input on balance, but similarly do not provide information on mobility, movement compensation, or specificity for exercise selection [124, 125]. Repetition maximums such as the 1-RM and 3-RM can help guide weight selection; however, the safety of this approach must be considered in both patients with cancer and novice individuals initiating a RT program for the first time. In these individuals, the authors of this article strongly recommend assessing movement patterns first (e.g., FMS), then confirming specific exercise movement patterns are followed safely and correctly prior to loading, and then slowly progressing weight load. Mobility and safety screening should be routinely performed to determine individualized exercise regimens while focusing on essential movement patterns. For example, participants with no mobility issues can perform the traditional barbell squat, while those with ankle mobility and dorsiflexion issues may engage in a modified variation such as the goblet squat. Participants with severe mobility issues may have to avoid the bilateral squat altogether and start with alternative or corrective exercises. This allows for stepwise progression once mobility issues have been adequately addressed through an individualized approach.

Last, as periodization and progression strategies are utilized with heavy and intense RT according to the individualized needs of the patient with cancer, direct observation with real-time modification is demonstrably effective in optimizing hypertrophy and BMD while ensuring safety [60]. Load calculations can provide insight into the effectiveness of the program and help further guide progression strategies. Additionally, motivating trainees to volitional fatigue and internal focus can enhance the hypertrophy benefits of RT [126]. However, the extent to which volitional fatigue outweighs other established RT principles (i.e., overload, specificity) is controversial and a current area of study. Direct observation of exercise programs is independently associated with enhanced strength gains, hypertrophy, and long-term regimen compliance [127, 128]. Limiting these exercise sessions to 60 min may avoid neuromuscular fatigue and the risk of injury [129]. Direct observation and training in group settings may aid in the difficult task of behavioral and motivational changes in these groups, particularly after cancer treatment, while providing additional safety benefits.

6 Conclusions

In summary, the benefits of exercise in the cancer treatment and survivorship setting are many. Optimal implementation of RT should target hypertrophy, BMD, strength, functional mobility, and body composition, which is best achieved through a series of individualized high-intensity compound movements that mirror functional mobility patterns, routinely performed over sessions limited to 60 min. Adequate stress on the musculoskeletal system is necessary to promote compensatory cellular mechanisms that improve the structural integrity of bones and muscles, stimulate metabolism and the immune system, promote a metabolic environment that minimizes excess adipose tissue, optimizes functional performance, and minimizes mechanical injury risk. The current evidence suggests that application of the above exercise principles, practiced in a safe environment under expert observation, may offer patients with cancer an effective means of improving both quality and quantity of life. The smaller effect of RT seen in cancer populations may be the result of many factors, including, but not limited to, the side effects of treatment, typical sequelae of the cancer diagnosis such as pain and mobility impairment. Future studies applying methods that incorporate the general RT techniques described above may help provide further insight.

The American College of Sports Medicine guidelines recommend 2–3 days/week of RT focused on large muscle groups utilizing loads of 60–70% 1 RM with 1–3 sets of 8–12 repetitions. However, optimizing the benefits of RT in patients with cancer may require a modification of these recommendations, with a focus on higher intensity and lower repetitions at a higher weight with compound movements. Additionally, patient-specific recommendations are vital because of the multitude of potential physical impairments from cancer types and treatments.

Resistance training within the cancer population poses unique challenges to engage individuals in programs that follow exercise principles to improve physical outcomes while ensuring safety. Reports on adherence rates have been excellent in prior studies, suggesting that optimizing RT regimens may provide an opportunity to improve overall health and cancer-specific outcomes.

Declarations

Funding No sources of funding were used to assist in the preparation of this article.

Conflicts of interest/Competing interests Colin Champ receives compensation from books that discuss nutrition and exercise and is a scientific advisor to Biosense and Atkins/Simply Good Foods. Jared Rosenberg, David Carpenter, Bradley Ackerson, Alexander Diaz, and Parker Hyde declare that they have no conflicts of interest relevant to the content of this review.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material No data are available for this article, as it is a narrative review.

Code availability Not applicable.

Authors' contributions CC wrote the first draft of the manuscript. JR, DC, BA, AD, and PH reviewed and edited the manuscript. All authors read and approved the final manuscript.

References

1. Lee K. Sarcopenic obesity and 10-year cardiovascular disease risk scores in cancer survivors and non-cancer participants using a nationwide survey. Eur J Cancer Care. 2020. https://doi.org/10.1111/ecc.13365.
2. Edwards BJ, Sun M, Zhang X, Holmes HM, Song J, Khalil P, et al. Fractures frequently occur in older cancer patients: the MD Anderson Cancer Center experience. Support Care Cancer. 2018;26:1561–8.
3. Mejdahl MK, Andersen KG, Gärtner R, Kroman N, Kehlet H. Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. BMJ. 2013;346:f1865.
4. Mohile SG, Xian Y, Dale W, Fisher SG, Rodin M, Morrow GR, et al. Association of a cancer diagnosis with vulnerability and frailty in older Medicare beneficiaries. J Natl Cancer Inst. 2009;101:1206–15.
5. Christensen JF, Jones LW, Andersen JL, Daugaard G, Rorth M, Hojman P. Muscle dysfunction in cancer patients. Ann Oncol. 2014;25:947–58.
6. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31:1539–47.
7. Anjanappa M, Corden M, Green A, Roberts D, Hoskin P, McWilliam A, et al. Sarcopenia in cancer: risking more than muscle loss. Tech Innov Patient Support Radiat Oncol. 2020;16:50–7.
8. Fairman CM, Focht BC, Lucas AR, Lustberg MB. Effects of exercise interventions during different treatments in breast cancer. J Community Support Oncol. 2016;14:200–9.
9. Rosenberg J, Hyde PN, Yancy WS, Ford KM, Champ CE. Quantity of resistance exercise for breast cancer patients: does the dose match the objective? J Strength Cond Res. 2021;35:1467–76.
10. Singh B, Spence RR, Steele ML, Sandler CX, Peake JM, Hayes SC. A systematic review and meta-analysis of the safety, feasibility, and effect of exercise in women with stage II+ breast cancer. Arch Phys Med Rehabil. 2018;99:2621–36.
11. Clifford B, Koizumi S, Wewege MA, Leake HB, Ha L, Macdonald E, et al. The effect of resistance training on body composition during and after cancer treatment: a systematic review and meta-analysis. Sport Med. 2021;26.
12. Schmitz KH, Troxel AB, Cheville A, Grant LL, Bryan CJ, Gross CR, et al. Physical activity and lymphedema (the PAL trial): assessing the safety of progressive strength training in breast cancer survivors. Contemp Clin Trials. 2009;30:233–45.
13. Fairman CM, Hyde PN, Focht BC. Resistance training interventions across the cancer control continuum: a systematic review of the implementation of resistance training principles. Br J Sports Med. 2017;51:677–85.
14. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, et al. Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med. 2009;361:664–73.
15. Kirkham AA, Bland KA, Zucker DS, Bovard J, Shenkier T, McKenzie DC, et al. "Chemotherapy-periodized" exercise to accommodate for cyclical variation in fatigue. Med Sci Sports Exerc. 2020;52:278–86.
16. Dawson JK, Dorff TB, Tuzon C, Rice JC, Schroeder ET, Lane CJ, et al. Effect of periodized resistance training on skeletal muscle during androgen deprivation therapy for prostate cancer: a pilot randomized trial. Integr Cancer Ther. 2021;20:153473542110354.
17. Fairman CM, Zourdos MC, Helms ER, Focht BC. A scientific rationale to improve resistance training prescription in exercise oncology. Sports Med. 2017;47:1457–65.
18. Latella C, Peddle-McIntyre C, Marcotte L, Steele J, Kendall K, Fairman CM. Strengthening the case for cluster set resistance training in aged and clinical settings: emerging evidence, proposed benefits and suggestions. Sports Med. 2021;51:1335–51.
19. Champ CE, Rosenberg J, Nakfoor BM, Hyde PN. Comment on "The Effect of Resistance Training on Body Composition During and After Cancer Treatment: A Systematic Review and Meta-analysis". Sports Med. 2021;52:1721–2.
20. Champ CE, Yancy WS. Exercise and patients with cancer: is it time to get heavier with the dose? JAMA Oncol. 2020;6:301.
21. Saad F, Adachi JD, Brown JP, Canning LA, Gelmon KA, Josse RG, et al. Cancer treatment-induced bone loss in breast and prostate cancer. J Clin Oncol. 2008; p. 5465–76.
22. Visovsky C, Bovaird JA, Tofthagen C, Rice J. Heading off peripheral neuropathy with exercise. ClinicalTrials.gov. 2009;2:4/1/2009-6/1/2011.
23. Giordano SH, Lee A, Kuo YF, Freeman J, Goodwin JS. Late gastrointestinal toxicity after radiation for prostate cancer. Cancer. 2006;107:423–32.
24. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. Med Sci Sports Exerc. 2004;36:674–88.
25. American College of Sports Medicine. American College of Sports Medicine position stand: progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009;41:687–708.
26. Wilmore J. The aging of bone and muscle. Clin Sport Med. 1991;10:231–44.
27. Caan BJ, Cespedes Feliciano EM, Prado CM, Alexeeff S, Kroenke CH, Bradshaw P, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. JAMA Oncol. 2018;4:798.
28. Van Ancum JM, Pijnappels M, Jonkman NH, Scheerman K, Verlaan S, Meskers CGM, et al. Muscle mass and muscle strength are associated with pre- and post-hospitalization falls in older male inpatients: a longitudinal cohort study. BMC Geriatr. 2018;18:116.
29. Dev R, Bruera E, Dalal S. Insulin resistance and body composition in cancer patients. Ann Oncol. 2018;29:ii18-26.
30. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes: findings from the Third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab. 2011;96:2898–903.
31. Shaw CS, Swinton C, Morales-Scholz MG, McRae N, Erftemeyer T, Aldous A, Murphy RMHK. The impact of exercise training status on the fibre type specific abundance of proteins regulating intramuscular lipid metabolism. J Appl Physiol. 2020;128:379–89.
32. Korhonen MT, Cristea A, Alén M, Häkkinen K, Sipilä S, Mero A, et al. Aging, muscle fiber type, and contractile function in sprint-trained athletes. J Appl Physiol. 2006;101:906–17.
33. Thelen DG, Schultz AB, Alexander NB, Ashton-Miller JA. Effects of age on rapid ankle torque development. J Gerontol A Biol Sci Med Sci. 1996;51:226–32.
34. Grgic J, Schoenfeld BJ. Are the hypertrophic adaptations to high and low-load resistance training muscle fiber type specific? Front Physiol. 2018;9:402.

35. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10:90–9.
36. Kamel FAH, Basha MA, Alsharidah AS, Salama AB. Resistance training impact on mobility, muscle strength and lean mass in pancreatic cancer cachexia: a randomized controlled trial. Clin Rehabil. 2020;34:1391–9.
37. Pedersen BK. Muscles and their myokines. J Exp Biol. 2011;214:337–46.
38. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010;24:2857–72.
39. Vierck J, O'Reilly B, Hossner K, Antonio J, Byrne K, Bucci L, et al. Satellite cell regulation following myotrauma caused by resistance exercise. Cell Biol Int. 2000;24:263–72.
40. McCormick KM, Schultz E. Role of satellite cells in altering myosin expression during avian skeletal muscle hypertrophy. Dev Dyn. 1994;199:52–63.
41. Crameri RM, Langberg H, Magnusson P, Jensen CH, Schrøoder HD, Olesen JL, et al. Changes in satellite cells in human skeletal muscle after a single bout of high intensity exercise. J Physiol. 2004;558:333–40.
42. Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat Cell Biol. 2001;3:1014–9.
43. Serrano AL, Baeza-Raja B, Perdiguero E, Jardí M, Muñoz-Cánoves P. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. Cell Metab Cell Metab. 2008;7:33–44.
44. Hornberger TA, Esser KA. Mechanotransduction and the regulation of protein synthesis in skeletal muscle. Proc Nutr Soc. 2004;63:331–5.
45. Tipton KD, Wolfe RR. Exercise, protein metabolism, and muscle growth. Int J Sport Nutr. 2001; p. 109–32.
46. Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High-intensity strength training in nonagenarians: effects on skeletal muscle. JAMA. 1990;263:3029–34.
47. Schoenfeld BJ. Is there a minimum intensity threshold for resistance training-induced hypertrophic adaptations? Sports Med. 2013;43:1279–88.
48. Schoenfeld BJ, Ogborn D, Krieger JW. Dose-response relationship between weekly resistance training volume and increases in muscle mass: a systematic review and meta-analysis. J Sports Sci. 2017;35:1073–82.
49. Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW. Strength and hypertrophy adaptations between low- vs. high-load resistance training: a systematic review and meta-analysis. J Strength Cond Res. 2017; p. 3508–23.
50. Oh HJ, Yoon BH, Ha YC, Suh DC, Lee SM, Koo KH, et al. The change of bone mineral density and bone metabolism after gastrectomy for gastric cancer: a meta-analysis. Osteoporos Int. 2020;31:267–75.
51. Sattui SE, Saag KG. Fracture mortality: associations with epidemiology and osteoporosis treatment. Nat Rev Endocrinol. 2014;10:592–602.
52. Frost HM. Bone "mass" and the "mechanostat": a proposal. Anat Rec. 1987;219:1–9.
53. Frost HM. Skeletal structural adaptations to mechanical usage (SATMU): 1. Redefining Wolff's law: the bone modeling problem. Anat Rec. 1990;226:403–13.
54. Frost HM. A determinant of bone architecture: the minimum effective strain. Clin Orthop Relat Res. 1983;175:286–92.
55. Turner CH. Three rules for bone adaptation to mechanical stimuli. Bone. 1998;23:399–407.
56. Calatayud J, Borreani S, Moya D, Colado JC, Triplett NT. Exercise to improve bone mineral density. Strength Cond J. 2013;35:70–4.
57. Brentano MA, Cadore EL, Da Silva EM, Ambrosini AB, Coertjens M, Petkowicz R, et al. Physiological adaptations to strength and circuit training in postmenopausal women with bone loss. J Strength Cond Res. 2008;22:1816–25.
58. Chilibeck PD, Sale DG, Webber CE. Exercise and bone mineral density. Sports Med. 1995;2:103–22.
59. Mosti MP, Kaehler N, Stunes AK, Hoff J, Syversen U. Maximal strength training in postmenopausal women with osteoporosis or osteopenia. J Strength Cond Res. 2013;27:2879–86.
60. Watson SL, Weeks BK, Weis LJ, Harding AT, Horan SA, Beck BR. High-intensity resistance and impact training improves bone mineral density and physical function in postmenopausal women with osteopenia and osteoporosis: the LIFTMOR randomized controlled trial. J Bone Miner Res. 2018;33:211–20.
61. Bousson V, Le Bras A, Roqueplan F, Kang Y, Mitton D, Kolta S, et al. Volumetric quantitative computed tomography of the proximal femur: relationships linking geometric and densitometric variables to bone strength. Role for compact bone. Osteoporos Int. 2006;17:855–64.
62. Cussler EC, Lohman TG, Going SB, Houtkooper LB, Metcalfe LL, Flint-Wagner HG, et al. Weight lifted in strength training predicts bone change in postmenopausal women. Med Sci Sports Exerc. 2003;35:10–7.
63. Kerr D, Morton A, Dick I, Prince R. Exercise effects on bone mass in postmenopausal women are site-specific and load-dependent. J Bone Miner Res. 1996;11:218–25.
64. Von SS, Kemmler W, Pintag R, Beeskow C, Weineck J, Lauber D, et al. Power training is more effective than strength training for maintaining bone mineral density in postmenopausal women. J Appl Physiol. 1985;2005(99):181–8.
65. Nguyen HG, Pham MT, Ho-Pham LT, Nguyen TV. Lean mass and peak bone mineral density. Osteoporos Sarcopenia. 2020;6:212–6.
66. Creighton DL, Morgan AL, Boardley D, Gunnar BP. Weight-bearing exercise and markers of bone turnover in female athletes. J Appl Physiol. 2001;90:565–70.
67. Lohman T, Going S, Hall M, Ritenbaugh C, Bare L, Hill A, et al. Effects of resistance training on regional and total bone mineral density in premenopausal women: a randomized prospective study. J Bone Miner Res. 1995;10:1015–24.
68. Winters-Stone KM, Dobek JC, Bennett JA, Maddalozzo GF, Ryan CW, Beer TM. Skeletal response to resistance and impact training in prostate cancer survivors. Med Sci Sports Exerc. 2014;46:1482–8.
69. Newton RU, Galvão DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Exercise mode specificity for preserving spine and hip bone mineral density in prostate cancer patients. Med Sci Sports Exerc. 2019;51:607–14.
70. Winters-Stone KM, Dobek J, Nail LM, Bennett JA, Leo MC, Torgrimson-Ojerio B, et al. Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. Osteoporos Int. 2013;24:1637–46.
71. Cypess AM. Reassessing human adipose tissue. N Engl J Med. 2022;386:768–79.
72. O'Rourke RW. Adipose tissue and the physiologic underpinnings of metabolic disease. Surg Obes Relat Dis. 2018;11:1755–63.
73. De Onis M, Habicht JP. Anthropometric reference data for international use: Recommendations from a World Health Organization Expert Committee. Am J Clin Nutr. 1996;64:650–8.
74. McArdle WD, Katch Frank L, Katch Victor L. Essentials of exercise physiology. Third Edition. Lippincott Williams, &

Wilkins; 2006. https://books.google.it/books/about/Essentials_of_Exercise_Physiology.html?id=L4aZIDbmV3oC&redir_esc=y. Accessed 14 Mar 2022.
75. Yarizadeh H, Eftekhar R, Anjom-Shoae J, Speakman JR, Djafarian K. The effect of aerobic and resistance training and combined exercise modalities on subcutaneous abdominal fat: a systematic review and meta-analysis of randomized clinical trials. Adv Nutr. 2021; p. 179–96.
76. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359–86.
77. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The impact of obesity on breast cancer diagnosis and treatment. Curr Oncol Rep. 2019;21:1–6.
78. Petrelli F, Cortellini A, Indini A, Tomasello G, Ghidini M, Nigro O, et al. Association of obesity with survival outcomes in patients with cancer: a systematic review and meta-analysis. JAMA Netw Open. 2021;4:3.
79. Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006;24:3979–83.
80. Wewege MA, Desai I, Honey C, Coorie B, Jones MD, Clifford BK, et al. The effect of resistance training in healthy adults on body fat percentage, fat mass and visceral fat: a systematic review and meta-analysis. Sport Med. 2022;52:287–300.
81. Ligibel JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA, Chlebowski RT, et al. American Society of Clinical Oncology position statement on obesity and cancer. J Clin Oncol. 2014;32:3568–74.
82. Khow KSF, Visvanathan R. Falls in the aging population. Clin Geriatr Med. 2017;33:357–68.
83. Ko SU, Simonsick EM, Deshpande N, Studenski S, Ferrucci L. Ankle proprioception-associated gait patterns in older adults: results from the Baltimore longitudinal study of aging. Med Sci Sports Exerc. 2016;48:2190–4.
84. de Resende-Neto AG, do Nascimento MA, de Sá CA, Ribeiro AS, Desantana JM, da Silva-Grigoletto ME. Comparison between functional and traditional training exercises on joint mobility, determinants of walking and muscle strength in older women. J Sports Med Phys Fitness. 2019; 59:1659–68.
85. Kozlenia D, Domaradzki J. Prediction and injury risk based on movement patterns and flexibility in a 6-month prospective study among physically active adults. PeerJ. 2021;18:9.
86. Liu CJ, Shiroy DM, Jones LY, Clark DO. Systematic review of functional training on muscle strength, physical functioning, and activities of daily living in older adults. Eur Rev Aging Phys Act. 2014;11:95–106.
87. Stensdotter A-KK, Hodges PWPW, Mellor R, Sundelin G, Hager-Ross C, Häger-Ross C. Quadriceps activation in closed and in open kinetic chain exercise. Med Sci Sports Exerc. 2003;35:2043–7.
88. Kim MK, Yoo KT. The effects of open and closed kinetic chain exercises on the static and dynamic balance of the ankle joints in young healthy women. J Phys Ther Sci. 2017;29:845–50.
89. Thabet AAEM, Alshehri MA, Helal OF, Refaat B. The impact of closed versus open kinetic chain exercises on osteoporotic femur neck and risk of fall in postmenopausal women. J Phys Ther Sci. 2017;29:1612–6.
90. Focht BC, Clinton SK, Lucas AR, Saunders N, Grainger E, Thomas-Ahner JM. Effects of exercise on disablement process model outcomes in prostate cancer patients undergoing androgen deprivation therapy. J Community Support Oncol. 2014;12:278–92.
91. De Vreede PL, Samson MM, Van Meeteren NLU, Duursma SA, Verhaar HJJ. Functional-task exercise versus resistance strength exercise to improve daily function in older women: a randomized, controlled trial. J Am Geriatr Soc. 2005;53:2–10.
92. Hamlyn N, Behm DG, Young WB. Trunk muscle activation during dynamic weight-training exercises and isometric instability activities. J Strength Cond Res. 2007;21:1108–12.
93. Schwanbeck S, Chilibeck PD, Binsted G. A comparison of free weight squat to Smith machine squat using electromyography. J Strength Cond Res. 2009;23:2588–91.
94. Swinton PA, Lloyd R, Keogh JWL, Agouris I, Stewart AD. A biomechanical comparison of the traditional squat, powerlifting squat, and box squat. J Strength Cond Res. 2012;26:1805–16.
95. Botton CE, Radaelli R, Wilhelm EN, Rech A, Brown LE, Pinto RS. Neuromuscular adaptations to unilateral vs. bilateral strength training in women. J Strength Cond Res. 2016;30:1924–32.
96. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med. 1994;330:1769–75.
97. Paton CD, Hopkins WG. Combining explosive and high-resistance training improves performance in competitive cyclists. J Strength Cond Res. 2005;19:826–30.
98. Adams K, O'Shea JP, O'Shea KL, Climstein M. The effect of six weeks of squat, plyometric and squat-plyometric training on power production. J Strength Cond Res. 1992;6:36–41.
99. Raymond MJ, Bramley-Tzerefos RE, Jeffs KJ, Winter A, Holland AE. Systematic review of high-intensity progressive resistance strength training of the lower limb compared with other intensities of strength training in older adults. Arch Phys Med. Rehabil. 2013;94:1458–72.
100. Schoenfeld B, Grgic J. Evidence-based guidelines for resistance training volume to maximize muscle hypertrophy. Strength Cond J. 2018;40:107–12.
101. Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High-intensity strength training in nonagenarians. JAMA. 1990;263:3029–34.
102. Seynnes O, Fiatarone Singh MA, Hue O, Pras P, Legros P, Bernard PL. Physiological and functional responses to low-moderate versus high-intensity progressive resistance training in frail elders. J Gerontol A Biol Sci Med Sci. 2004;59:M503–9.
103. Stasinaki AN, Gloumis G, Spengos K, Blazevich AJ, Zaras N, Georgiadis G, et al. Muscle strength, power, and morphologic adaptations after 6 weeks of compound vs. complex training in healthy men. J Strength Cond Res. 2015;29:2559–69.
104. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8:201–17.
105. Nieman DC. Is infection risk linked to exercise workload? Med Sci Sports Exerc. 2000;32:406–11.
106. Larrabee RC. Leucocytosis after violent exercise. J Med Res. 1902;7:76–82.
107. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the regulation of immune functions. Prog Mol Biol Transl Sci. 2015;135:355–80.
108. Adams GR, Zaldivar FP, Nance DM, Kodesh E, Radom-Aizik S, Cooper DM. Exercise and leukocyte interchange among central circulation, lung, spleen, and muscle. Brain Behav Immun. 2011;25:658–66.
109. Rall LC, Roubenoff R, Cannon JG, Abad LW, Dinarello CA, Meydani SN. Effects of progressive resistance training on immune response in aging and chronic inflammation. Med Sci Sports Exerc. 1996;28:1356–65.
110. Winters-Stone KM, Wood LJ, Stoyles S, Dieckmann NF. The effects of resistance exercise on biomarkers of breast cancer

prognosis: a pooled analysis of three randomized trials. Cancer Epidemiol Biomark Prev. 2018;27:146–53.
111. Freidenreich D, Volek J. Immune responses to resistance exercise. Exerc Immunol Rev. 2012;18:8–41.
112. Pontzer H, Yamada Y, Sagayama H, Ainslie PN, Andersen LF, Anderson LJ, et al. Daily energy expenditure through the human life course. Science. 2021;373:2021.
113. Manini TM. Energy expenditure and aging. Ageing Res. 2010;9:1–11.
114. Speakman JR, Selman C. Physical activity and resting metabolic rate. Proc Nutr Soc. 2003;62:621–34.
115. Osterberg KL, Melby CL. Effect of acute resistance exercise on postexercise oxygen consumption and resting metabolic rate in young women. Int J Sport Nutr Exerc Metab. 2000;10:71–81.
116. Gillette CA, Bullough RC, Melby CL. Postexercise energy expenditure in response to acute aerobic or resistive exercise. Int J Sport Nutr. 1994;4:347–60.
117. Baker EJ, Gleeson TT. The effects of intensity on the energetics of brief locomotor activity. J Exp Biol. 1999;202:3081–7.
118. Kraemer W, Noble B, Clark M, Culver B. Physiologic responses to heavy-resistance exercise with very short rest periods. Int J Sports Med. 1987;8:247–52.
119. Bland KA, Kouw IWK, van Loon LJC, Zopf EM, Fairman CM. Exercise-based interventions to counteract skeletal muscle mass loss in people with cancer: can we overcome the odds? Sport Med. 2022;52:1009–27.
120. Bonazza NA, Smuin D, Onks CA, Silvis ML, Dhawan A. Reliability, validity, and injury predictive value of the Functional Movement Screen. Am J Sports Med. 2017;45:725–32.
121. Beardsley C, Contreras B. The functional movement screen. Strength Cond J. 2014;36:72–80.
122. Cook G, Burton L, Hoogenboom B. Pre-participation screening: the use of fundamental movements as an assessment of function—part 2. N Am J Sports Phys Ther. 2006;1:132–9.
123. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–7.
124. Mathias S, Nayak U, Isaacs B. Balance in elderly patients: the "get-up and go" test. Arch Phys Med Rehabil. 1986;67:387–9.
125. Whitney SL, Wrisley DM, Marchetti GF, Gee MA, Redfern MS, Furman JM. Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the five-times-sit-to-stand Test. Phys Ther. 2005;85:1034–45.
126. Morton RW, Colenso-Semple L, Phillips SM. Training for strength and hypertrophy: an evidence-based approach. Curr Opin Physiol. 2019;10:90–5.
127. Mazzetti SA, Kraemer WJ, Volek JS, Duncan ND, Ratamess NA, Gómez AL, et al. The influence of direct supervision of resistance training on strength performance. Med Sci Sport Exerc. 2000;32:1175–84.
128. Grimmett C, Corbett T, Brunet J, Shepherd J, Pinto BM, May CR, et al. Systematic review and meta-analysis of maintenance of physical activity behaviour change in cancer survivors. Int J Behav Nutr Phys Act. 2019;16:37.
129. Aagaard P, Suetta C, Caserotti P, Magnusson SP, Kjær M. Role of the nervous system in sarcopenia and muscle atrophy with aging: strength training as a countermeasure. Scand J Med Sci Sport. 2010;20:49–64.