2019

The potential therapeutic effects of creatine supplementation on body composition and muscle function in cancer

C M. Fairman

K L. Kendall

Nicolas H. Hart
The University of Notre Dame Australia, nicolas.hart@nd.edu.au

D R. Taaffe

D A. Galvao

See next page for additional authors

This article was originally published as:
Fairman, C. M., Kendall, K. L., Hart, N. H., Taaffe, D. R., Galvao, D. A., & Newton, R. U. (2019). The potential therapeutic effects of creatine supplementation on body composition and muscle function in cancer. *Critical Reviews in Oncology Hematology, 133*, 46-57.

Original article available here:
10.1016/j.critrevonc.2018.11.003

This is the accepted manuscript version of an editorial published as:

Fairman, C.M., Kendall, K.L., Hart, N.H., Taaffe, D.R., Galvao, D.A., and Newton, R.U. (2019) The potential therapeutic effects of creatine supplementation on body composition and muscle function in cancer. *Critical Reviews in Oncology Hematology, 133,* 46-57. doi: 10.1016/j.critrevonc.2018.11.003

This article has been published in final form at https://doi.org/10.1016/j.critrevonc.2018.11.003

The therapeutic role of creatine supplementation to treat musculoskeletal toxicity in cancer

Fairman CM[1,2], Kendall KL[2], Hart NH[1,2,3], Taaffe DR[1,2,4], Galvão DA[1,2], Newton RU[1,2,4]

From:

1. Exercise Medicine Research Institute, Edith Cowan University, Perth, Western Australia, Australia

2. School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia

3. Institute for Health Research, University of Notre Dame Australia, Perth, Western Australia, Australia

4. School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Queensland, Australia

Corresponding Author:
Dr Ciaran Fairman
Exercise Medicine Research Institute
Edith Cowan University
270 Joondalup Drive, JOONDALUP
Perth, WA, Australia, 6027.

Email: c.fairman@ecu.edu.au
Phone: +61 8 6304 3672

***Running Title*:** Creatine to treat muscle-bone cancer toxicity

The therapeutic role of creatine supplementation to treat musculoskeletal toxicity in cancer

Abstract

Low muscle mass in individuals with cancer has a profound impact on quality of life and independence, and is associated with greater treatment toxicity and poorer prognosis. Exercise interventions are regularly being investigated as a means to ameliorate treatment-related adverse effects, and nutrional/supplementation strategies to augment adaptations to exercise are highly valuable. Creatine (Cr) is a naturally-occurring substance in the human body that plays a critical role in energy provision during muscle contraction. Given the beneficial effects of Cr supplementation on lean body mass, strength, and physical function in a variety of clinical populations, there is therapeutic potential in individuals with cancer at heightened risk for muscle loss. Here, we provide an overview of Cr physiology, summarize the evidence on the use of Cr supplementation in various aging/clinical populations, explore mechanisms of action, and provide perspectives on the potential therapeutic role of Cr in the exercise oncology setting.

Keywords: oncology, cachexia, body composition, muscle, bone, strength, resistance training,

1.Introduction

Individuals with cancer are at a high risk of skeletal muscle wasting that may be exacerbated by tumor-related factors and cancer therapies (certain hormone and chemotherapies in particular) [1-7]. An emerging body of literature supports the role of exercise as a means to ameliorate these treatment-related declines and improve clinically relevant patient outcomes [7-10]. Indeed, the existing evidence is that progressive resistance training (PRT) can improve physical function, muscle strength and body composition in patients undergoing a variety of treatments [10-16]. Nevertheless, given the implications of low muscle mass on treatment toxicity and prognosis, identifying strategies to enhance adaptations to exercise training in a cancer population are of both clinical benefit and importance [17-20]. More recently, there has been an increasing appreciation for the role of nutritional and dietary supplement interventions, both alone and with exercise, to maintain or improve clinically relevant outcomes and augment training adaptations in cancer patients [21-24].

Creatine (Cr) is one of the most extensively studied supplements, with research demonstrating its efficacy to augment lean body mass (LBM) accretion, increase muscle strength, and improve physical function in a variety of healthy and clinical populations [25]. More recently, Cr supplementation has gained attention in the medical field as a result of the beneficial effects found in numerous muscular and neurological diseases, such as McArdle disease, Duchenne dystrophy, myasthenis gravis, amyotrophic lateral sclerosis, and Parkinson's disease [17, 26, 27]. Given the potent additive effects of Cr on muscle performance and LBM, it's unsurprising that Cr is now being considered as a therapeutic aid in some cancer contexts [28]. Nevertheless, supplementation with Cr in a cancer context, particularly in human participants, is notably sparse. Paucity of

research in this area may stem from lack of awareness of the potential role of Cr supplementation in a cancer setting, misunderstanding of mechanisms of action, safety concerns from unfounded media reports, or a combination of the above. Thus, the purpose of this narrative review is to provide: (1) an overview of Cr physiology; (2) summarize studies investigating the therapeutic use of Cr supplementation in cancer and other clinical populations; (3) provide perspectives on the potential therapeutic role of Cr supplementation to treat cancer-related physical impairments, (4) identify specific types of cancer groups that may benefit the most from supplementation and (5) offer suggestions for future research.

2.Creatine metabolism

Cr is a naturally-occurring substance in the human body, synthesized endogenously in the kidneys, pancreas and liver at a rate of ~1-2 g/day [29]. Additionally, approximately 1 gram of Cr can be consumed by individuals with a diet high in meat and fish [30]. The majority of Cr (95%) is stored in skeletal muscle (as free creatine or phosphocreatine), with the rest found in the brain and testes [25]. Approximately 2 g/day of Cr is lost as creatinine in urine. Given that rates of excretion typically match levels of endogenous production and intake, the most efficient way to increase intramuscular Cr stores is through supplementation [30].

Cr is a component of the high-energy phosphate, phosphocreatine (PCr), which plays a critical role in rapid energy provision during skeletal muscle contraction [21]. Re-phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP) during and following exercise (Figure 1) is reliant on the amount of PCr stored in the muscle (PCr + ADP $\leftrightarrow$ Cr + ATP) [25].

In addition to its role as a temporal energy buffer, PCr acts as a spatial energy buffer to shuttle high-energy phosphates between mitochondria and cellular ATP utilization sites [31].

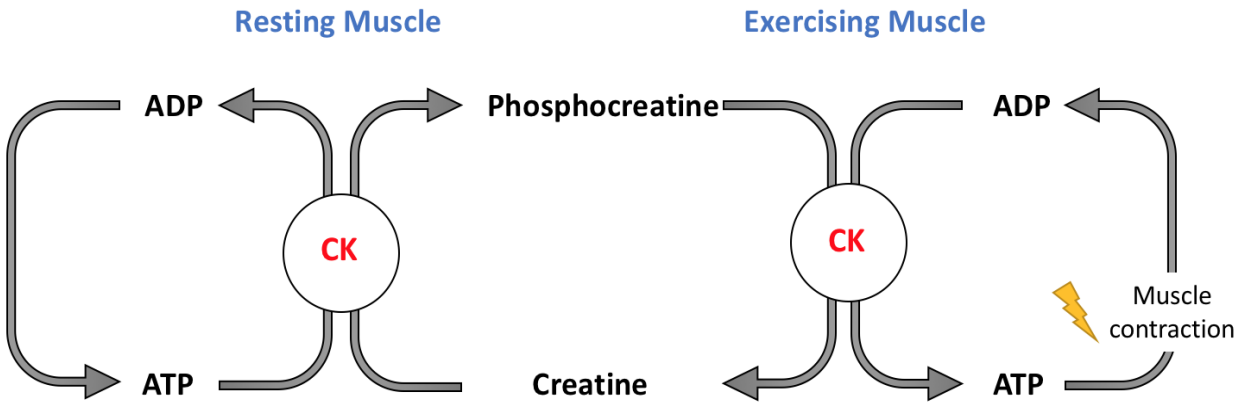

Fig 1. Phosphocreatine shuttle system. Creatine catalyzes reversible phosphorylation of creatine to Phosphocreatine and ADP to ATP. (print in color)

It is hypothesized that Cr uptake by skeletal muscle is modulated by muscle activity [32]. As PCr availability diminishes with intense exercise, ability to sustain exercise effort declines accordingly. Further, an increase in availability of PCr may allow for accelerated resynthesis of ATP during exercise [25, 33]. In this manner, PCr content in the muscle may be an important regulator of exercise capacity. As a result, the ergogenic effects of Cr supplementation are likely an increase in intramuscular PCr [32, 34], enhancing exercise capacity, and leading to an increase in training quality and overall training volume [25, 33]. In other words, an increase in the body's Cr stores may allow for better recovery between sets of exercises or repeated efforts, allowing the individual to perform more higher quality work and receive a better "dose" of exercise. When done consistently, this can add up to potentially greater improvements in LBM and strength compared to exercise alone.

3.Creatine supplementation in healthy aging/clinical populations

This section is not intended to be an exhaustive review of the relevant literature examining Cr supplementation in healthy aging/clinical populations. Rather, it is intended to outline the efficacy of Cr supplementation using select studies representative of the broader body of literature in improving relevant cancer-related outcomes (sarcopenia, loss of strength, bone health and physical function) that are experienced in other populations. Studies were chosen based on research design (randomised, double-blind, placebo-controlled), form of creatine used (creatine monohydrate), population being studied (clinical patients and older adults), and dependent variable reported (body composition and physical function). Indeed, more comprehensive reviews of Cr supplementation are available in healthy aging [35-37], neurodegenerative [36, 38] and muscular disorders [39].

3.1Healthy aging

Aging is associated with an incremental loss in muscle mass, physical function, and independence. Additionally, intramuscular stores of creatine are ~25% lower in older [40] and middle-aged adults [41] than younger individuals. However, individuals with low intramuscular total Cr concentrations show an enhanced ability to increase creatine content following Cr supplementation [32]. Cr supplementation has been shown to increase muscle strength and function, enhance fatigue resistance, and improve performance in activities of daily living irrespective of exercise training in older populations [42, 43]. A summary of the studies discussed in this review examining Cr supplementation in healthy aging/clinical populations are presented in Table 1.

Stout et al. [42] found significant increases in handgrip strength and physical working capacity among elderly men and women supplementing with Cr for 14 days. The significant delay in the

onset of neuromuscular fatigue, as measured by the physical working capacity (PWCFT) test, may have been due to elevated muscle PCr content, which can decrease the reliance on anaerobic glycolysis, reduce intramuscular lactate and ammonia accumulation, and therefore delay fatigue. Short-term Cr supplementation has also been shown to improve upper and lower body muscular strength. Gotshalk et al. [44] reported significant increases in bench press (4.1±1.4 kg) and leg press (16.1±4.4 kg) strength, as well as significant improvements in lower body mean power and timed sit-to-stand following 7 days of Cr supplementation in older men [45]. Supporting these findings, Canete et al. [44] demonstrated a 12% improvement in timed sit-to-stand following 7 days of Cr supplementation in older women.

Cr supplementation in conjunction with PRT can result in greater adaptations in skeletal muscle as compared with PRT alone. Multiple studies have shown greater improvements in strength when Cr supplementation is combined with whole body PRT in older adults [49-51]. Results from a meta-analysis undertaken by Devries and Phillips [37] indciated that Cr supplementation during PRT enhanced the gain in LBM, strength, and functional performance over PRT alone in older adults. Similarly, Brose and colleagues [46] reported significant increases in total body mass, fat-free mass, and isometric knee extension strength following 14 weeks of whole body resistance training plus Cr supplementation. Furthermore, after a six-month randomized controlled trial, researchers reported that Cr supplementation combined with PRT significantly increased appendicular lean mass, maximal strength, and muscle function to a greater extent than PRT alone in vulnerable older adults [47].

Cr supplementation combined with PRT also has beneficial effects on bone health. In older men, 10 weeks of Cr supplementation (0.1g/kg) combined with a structured PRT completed three times per week led to a significant reduction in bone resorption by 30% (assessed using the bone biomarker NTx), compared to a non-significant increase of 13% in the placebo group [48]. These results support previous findings from Chilibeck et al. [49], showing Cr supplementation (0.3g/kg for 5 days, 0.07g/kg for 79 days) during 12 weeks of supervised PRT in healthy older males significantly increased upper-limb bone mineral content (BMC) by 3.2%, compared to a non-significant decrease in the placebo group. Given that bone turnover is a relatively slow process typically requiring 9 months to detect changes [50, 51], these findings are somewhat remarkable.

While several studies have indicated potential benefits from Cr supplementation on bone health, others have found no effect. Lobo et al. [52] investigated the effects of long-term, low-dose Cr supplementation (1g/day) without exercise for 52 weeks on bone health in postmenopausal women and found that Cr had no greater effect on bone mineral density (BMD) or bone microarchitecture compared to placebo. Additionally, Gualano et al. [47] showed no additional benefit of Cr supplementation (20 g/day for 5 days + 5 g/day for 24 weeks) to PRT on lumbar spine, proximal femur or whole body BMD, or serum bone markers in postmenopausal women. Further, Brose et al. [50] found no effect from Cr supplementation (5g/day) on serum osteocalcin (indicator of bone formation) in healthy older men following a 14-week PRT program. As it stands, results are mixed in relation to Cr and bone health. Notably, studies employing higher volumes of resistance training (i.e. greater number of sets per muscle group per week) combined with Cr supplememtation appear to have a beneficial effect on LBM, muscle strength and physical function and bone health in older

adults [37]. However, longer term studies (>12 months) with rigourous methodology utilising higher training volume with Cr are warranted.

Table 1: Select studies examining the effects of Cr supplementation in healthy aging/clinical populations

Authors (year)	Patient/ subjects	Dosage	Protocol duration	Exercise program	Results	Adverse Effects
Healthy Aging						
Brose et al (2003) [46]	28 older adults	5 g/day + 2 g of dextrose	14 weeks	3 day/wk, 3 x 10 total body	↑ Total body mass; ↑ FFM; ↑ Iso knee ext.	None reported
Candow et al (2008)[48]	40 older men	0.10 g/kg/day	10 weeks	3 day/wk, 3 x 10 total body	↑ Upper body 1RM **; ↔ Lower body 1RM, ↓ 30% bone resorption, PLA ↑ 13% bone resorption	None reported
Stout et al (2007) [42]	15 older adults	20 g/day for 7 days then 10g/day	14 days of Cr v PLA with 4-6	n/a	Cr ↑ GRIP and PWCFT v PLA	None reported

			weeks crossover			
Gotshalk et al (2001) [45]	20 older men	0.3g/kg/day	7 days	n/a	↑ 1RM, ↑ LBP, ↓ STS, ↓ TG.	None reported
Chilibeck et al (2005)[49]	29 older men	0.3g/kg/day for 5 days, 0.07 g/kg/day for 79 days	12 weeks	3 day/wk, 3 x 10 total body	Cr ↑Upper limb BMC. ↔Legs, trunk or WB BMC.	None reported
Gualano et al (2014)[47]	60 older women	20 g/day for 5 days + 5 g/day for 24 weeks	24 weeks	2 day/wk, 3 x 8-12 total body	↔ Lumbar spine, proximal femur or WB BMD	None reported
Lobo et al (2015)[52]	109 post-menopausal, osteopenic women	1 g/day	12 months	n/a	↔ Lumbar spine, total hip or WB BMD	None reported
Gualano et al (2014)[47]	60 older women	20 g/day for 5 days + 5 g/day for 24 weeks	24 weeks	2 day/wk, 3 x 8-12 total body	↑ appendicular lean mass; ↔ fat mass.	None reported

Clinical Populations						
Andrews et al(1998) [53]	20 patients with chronic heart failure	20g/day	5 days	n/a	↑ contractions before fatigue at 75% MVC; ↓ lactate % ammonia at 75% MVC	None reported
Louis et al (2003)[54]	15 boys with MD	3g/day	3 months Cr and 3 months PLA separated by 2 months washout.	n/a	↑ MVC, TTE, BMD in ambulatory patients. ↓ urinary excretion of cross-linked N-telopeptides of Type I collagen	None reported
Tarnopolsky et al (2004)[55]	30 boys with MD	0.10 g/kg/day	4 months Cr and 4 months PLA separated by 6 week washout.	n/a	↓ urinary excretion of cross-linked N-telopeptides of Type I collagen**	None reported

Sakkas et al (2009)[56]	Patients with HIV infection	20 g/day for 5 days then 5g/day	12 weeks	3 day/wk, 4 x 8 total body	Greater ↑ LBM in Cr vs PLA.	None reported
Walter et al (2000) [87]	36 patients with muscular dystrophy	10.6 g/day for 10 days then 5 .3 g/day for 46 days	8 weeks	n/a	↑ muscle strength	None reported
Tarnopolsky et al (2004) [58]	30 boys with muscular dystrophy	0.10g/kg/day,	4-month supp, 6-week wash-out, 4 month PLA	n/a	↑ handgrip strength	n/a

BMC: Bone mineral content; BMD: Bone mineral density; BW: Bodyweight; Cr: creatine supplementation; g: gram; kg: kilogram; 1RM: 1 repetition maximum; FFM: Fat free mass; GRIP: maximal isometric grip strength; Iso: isometric; LBM: lean body mass; LBP: lower body power; MD: muscular dystrophy; MVW: maximum voluntary contraction; PWCFT: physical working capacity at fatigue threshold; PLA: placebo group; STS: sit-to-stand test; TG: tandem gait test; TTE: time to exhaustion; WB: whole body; n/a: not applicable; ↑: increase; ↓: decrease; ↔: no change; **compared to Placebo

3.2Clinical populations

Studies involving both human and animal models with various catabolic diseases have shown evidence of increased LBM, bone density, muscle strength, and exercise performance following Cr supplementation. HIV-infected persons often experience a loss of LBM [57], which has been associated with accelerated disease progression and increased morbidity. A 2009 study by Sakkas et al. [56] found that 14 weeks of Cr supplementation (20g/d for the first 5 days, followed by a maintenance dose of 4.8 g/day), combined with progressive PRT for 12 weeks produced a greater increase in LBM compared to the placebo + PRT group in patients with HIV infection.

Abnormalities of skeletal muscle in chronic heart failure patients include early onset of anaerobic metabolism and a swift depletion of PCr [58, 59]. In addition to abnormalities of PCr during exercise, patients with chronic heart failure have demonstrated a reduction in resting muscle Cr content and a delay in resynthesis of PCr post-exercise [60, 61]. Andrews et al. [53] examined the effects of Cr supplementation (20 g daily for 5 days) on repeated submaximal handgrip contractions in elderly men with chronic heart failure. The authors found a significant increase in the number of contractions performed before exhaustion at 75% maximum voluntary contraction (MVC) workload following Cr supplementation. Additionally, ammonia and lactate concentrations at the 75% MVC workload were significantly lower.

Muscular dystrophy is a genetic disease leading to muscle atrophy and bone loss. Researchers have examined the effects of three months of Cr supplementation (3g/day) in boys with Duchenne and Becker muscular dystrophy [54]. Participants in the Cr group who were able to walk during the intervention saw a significant decrease in urinary excretion of cross-linked N-telopeptides of Type

I collagen, an indicator of bone resorption, whereas participants in the placebo group experienced a 6% increase. Cr supplementation also increased lumbar spine and whole-body BMD (assessed via dual energy X-ray absorptiometry, DXA) by approximately 3.8% and 2%, respectively. No effect was found in wheelchair-dependent individuals. Given the length of the normal bone remodelling cycle, one could hypothesize an even greater increase in BMD following a longer intervention [51].

Tarnopolsky et al. [55] investigated the effects of Cr supplementation (0.1g/kg) in young boys with Duchenne muscular dystrophy for 4 months. Although no changes in whole body BMD or BMC were observed, Cr supplementation did attenuate the increase in urinary excretion of cross-linked N-telopeptides of Type I collagen by 22% compared to placebo. In addition, Kley et al. [62] conducted a meta-analysis on Cr and muscle disorders and concluded that Cr supplementation given to patients with muscular dystrophies led to significant increases in LBM, as well as maximum voluntary contraction, compared to placebo.

Differences in dosing, length of intervention, population being studied, and use of a PRT protocol may explain some of the discrepancies among studies. Taken collectively, results from the literature on Cr supplementation in healthy aging/clinical populations that demonstrate similar muscle wasting characteristics often experienced by cancer patients (sarcopenia and cachexia) indicate that Cr supplementation combined with PRT can result in superior improvements in muscle mass, muscle strength and physical function. These findings are promising, though more research is warranted to see if similar improvements are observed in individuals with cancer, particularly those at a heightened risk of muscle wasting.

4.Musculoskeletal dysfunction in cancer

Individuals with cancer are exposed to a variety of cancer-specific factors that result in decrements in muscle mass and function, such as tumor-related factors, cancer therapies (in particular certain hormone and chemotherapies), malnutrition, physical inactivity along with increasing age and comorbidities [1-6]. To date, the primary focus of research around muscle toxicity has been confined to cachexia. Importantly, sarcopenia is also a chief concern in this population, particularly given the implications of decreased muscle mass and strength on the incidence and prevalence of treatment toxicity and associations with poorer prognosis in lung cancer [63], colorectal cancer [64], pancreatic cancer [65, 66] and renal cell carcinoma [1, 63, 67]. Sarcopenia and cachexia are somewhat distinct in their etiology, though they can be interrelated in a cancer context whereby a sarcopenic patient can become cachectic, or cachexia can exacerbate sarcopenic symptoms, further depleting already low levels of muscle mass. Regardless, reductions in muscle mass and strength are associated with profound decrements in quality of life and independence, greater toxicity from treatment and all-cause mortality. The prevalence of muscle dysfunction varies based on the type and stage of cancer, treatment received and methodology of measurement.

4.1Sarcopenia

Sarcopenia refers to the age-related loss of muscle mass and function that typically accelerates with advancing age [3]. Characterized by changes in tissue quality, decreases in satellite cells, denervation and/or atrophy of type II muscle fibers and an increase in myosteatosis (fat infiltration in skeletal muscle); sarcopenia is associated with impairments in muscle strength, physical function and may increase the risk of falls [68-70]. Sarcopenia may be of particular relevance in

cancer, whereby many individuals are diagnosed at an older age, often presenting with sarcopenic characteristics at diagnosis. Prevalence of sarcopenia in different types of cancer and stages of disease has not been well defined in the oncology literature, likely compounded by lack of universal diagnostic criteria [3]. Nevertheless, prevalence of sarcopenia in individuals with cancer can range from 11-74% depending on the diagnostic criteria and methods of assessment [71-75].

4.2Cachexia

Cachexia is distinct from sarcopenia in that it is a more aggressive form of muscle wasting, characterized by profound, unintentional weight loss (muscle and fat mass) that cannot be fully ameliorated with nutritional interventions [5, 76, 77]. Indeed, development of cachexia further depletes already low muscle mass, thereby exacerbating the development of sarcopenia. Criteria for diagnosis of cachexia are a topic of ongoing discussion, though such criteria include weight loss >5% in the past 6 months [76]. A discussion of the mechanisms of cachexia is beyond the scope of this review, and for further information readers are referred to reviews by Tisdale [78] and Aoyagi et al. [79] Briefly, this severe muscle wasting syndrome is thought to be a result of a combination of factors, including systemic inflammation, tumor metabolism and tumor-mediated effects, along with malnutrition and physical inactivity [76]. Cachexia is a major cause of morbidity and mortality, and management of weight loss and cachectic symptoms are of high clinical importance to minimize the impact of this syndrome [76, 80].

4.3Body composition

Cancer treatments are also associated with poor body composition, through loss of muscle mass and/or increase in fat mass. Chemotherapy is regularly associated with increased adiposity during

treatment, with some studies demonstrating significant increases in body fat percentage up to a year following the cessation of treatment [81-86]. Accumulation of fat mass and/or loss of muscle mass have been documented in prostate cancer patients undergoing androgen deprivation therapy (ADT) [87-89]. Moreover, the use of corticosteroids to manage cancer and treatment side effects is associated with weight gain and redistribution of body fat [90]. Indeed, Cushingoid features (truncal obesity, dorsocervical and facial adiposity) can develop within the first two months of glucocorticoid therapy [90].

Several mechanisms for the adverse changes in body composition with cancer treatments have been proposed including lower levels of physical activity, development of menopause (in breast cancer), and treatment-related metabolic perturbations [84]. Importantly, there is increasing evidence that poor body composition and specifically, low muscle mass can increase severity of treatment toxicities [18-20]. Moreover, impairments in muscle mass can predispose individuals to a loss in physical function and the ability to perform activities of daily living, increase the risk of falls and fractures, leading to a reduction in independence and quality of life (QoL), and an increased risk of mortality [68-70, 91-94]. Clearly, identification of novel strategies to maintain or improve muscle mass and strength is of high priority and clinical importance.

There is strong evidence suggesting Cr supplementation can promote the overexpression of genes and proteins related to muscle hypertrophy [95, 96], as well as satellite cell activation [34]. Olsen et al. [34] reported that in healthy humans, Cr supplementation in combination with PRT amplified the increase in satellite cell number and myonuclei concentration in skeletal muscle fibers, thus facilitating muscle growth and hypertrophy. Cr has also been shown to enhance expression of

myogenin and other myogenic regulatory factors that regulate myosin heavy chain expression, affecting the contractile protein content (actin and myosin) [97]. The growth-promoting effects of Cr may be extremely useful in situations where anabolic activity is suppressed, such as muscle wasting diseases, ageing populations, and cancer patients.

4.4Bone health

Cancer induced bone loss is indicated in the majority of cancers, with a variety of interrelated factors from dietary and physical activity patterns, loss of muscle mass, cancer cells, cancer therapies (particularly chemotherapy and hormone therapy) and metastatic disease [98, 99]. Indeed, reductions in bone health compounds muscle wasting by contributing to the loss of overall lean body mass, poor physical functioning, and increased risk of fractures. Perturbations in the tightly coupled process of osteoclast-mediated bone resorption and osteoblast-mediated bone formation are common in a variety of cancers, particularly in a metastatic context, leading to a loss of structural integrity and subsequent skeletal complications [98, 100, 101]. This greater rate of bone turnover is likely due to an increase in osteoclast activity and bone resorption, coupled with a decrease in osteoblast activity (bone formation); though the inverse can also be true in some metastatic environments [98, 102-104]. Indeed, adverse changes in BMD coupled with a deterioration in bone quality and microarchitecture increases fracture risk due to heightened bone fragility.[98, 99, 103, 105, 106] Emerging evidence suggests Cr monohydrate may positively affect bone physiology, possibly by increasing the activity of osteoblast-like cells involved in bone formation [107, 108] and decreasing bone resorption.[48, 54, 55]

5.Cr supplementation in cancer patients

The few studies examining the effects of Cr in cancer patients have been mixed, with some showing no effect while others show some clinically meaningful benefit. A summary of these studies can be found in Table 2. Jatoi et al. [28] examined Cr supplementation in 263 colorectal cancer patients experiencing "anorexia/weight loss syndrome". In this trial, incurable patients were randomly assigned to either Cr (20g/day load x 5 days followed by 2 g/day) or placebo powder with identical dosing. Body weight was assessed weekly for one month and thereafter monthly while the patient remained on Cr or placebo. Appetite, QoL, and grip strength were also assessed. The primary endpoint was the percentage of patients who gained ≥10% of their baseline weight by 1 month. Out of 263 patients, only 3 gained ≥10% of their baseline weight over 1 month: two in the Cr group, and one in the placebo group. No significant differences in any of the measured variables were observed between the two groups. One possible explanation for lack of significant findings is the absence of a training stimulus. It is hypothesized that Cr uptake by skeletal muscle is modulated by muscle activity.[32] Muscle inactivity may contribute to a decrease in Cr uptake, and therefore compromise the effect of Cr supplementation on body weight and strength.

Table 2: Studies examining Cr supplementation in a cancer context.

Authors (year)	Patients	Dosage	Protocol duration	Exercise program	Results	Adverse Effects
Jatoi et al (2017)[28]	362 cancer patients with weight loss syndrome	20 g/day for 5 days then 2g/day	9 months	n/a	↔ body weight	None reported
Bourgeois et al (2008)[109]	Children with ALL undergoing chemotherapy	0.10 g/kg/day	2 x 16 weeks separated by 6 week wash-out period.	n/a	↓ BF% Cr, ↑ BF% NH ↔ BMD Cr	None reported
Norman et al (2008)[110]	Colorectal cancer patients undergoing chemotherapy	20g/day for 7 days then 5g/day	8 weeks	n/a	↑ body cell mass; ↑ cell integrity	None reported

Lonbro et al (2012)[23]	30 Head and neck patients treated with radiotherapy	5g/day + 30g Pro/day	12 weeks	3 day/wk, 3 x 10 total body	↑ LBM PROCR group,ns↑ PLA ↔ Muscle Strength** , ↔ Physical function**	None reported

ALL: acute lymphoblastic leukemia; BF%: body fat percentage; BMD: bone mineral density; Cr: creatine supplementation; g: gram; kg: kilogram; LBM: lean body mass NH: natural history group; PLA: placebo; PROCR: Protein + creatine supplementation; n/a: not applicable; ↑: increase; ↓: decrease; ↔: no change; **compared to Placebo.

Norman et al. [110] investigated the effects of 8 weeks of Cr supplementation on muscle function, body composition and QoL in colorectal cancer patients. Patients were randomized to receive either Cr monohydrate or a placebo. Patients in the Cr group received 20g/d for the first 7 days, followed by 5g/d as a maintenance for the remainder of the study. Following 8 weeks of supplementation, neither the Cr nor control group improved in assessments of body composition, muscle function, or QoL. Importantly, this study had no exercise component across the 8 weeks.

Bourgeois and colleagues [109] investigated the effects of Cr supplementation with children on maintenance chemotherapy for acute lymphoblastic leukemia for two periods of 16 weeks separated by a 6-week "wash out" period. Participants in this study were also subject to corticosteroid therapy as part of their cancer treatment. The authors found no effects of Cr supplementation on body weight, lumbar spine BMD, whole body BMC or LBM. However, Cr

supplementation was associated with a reduction in body fat in supplemented patients. This is an important clinical finding considering those in the control group experienced a significant increase in body fat across the duration of treatment. Lonbro et al.[23] examined feasibility and efficacy of 12 weeks of PRT in combination with protein and Cr supplementation (PROCR) in head and neck cancer patients.[23] Patients were randomized into two groups: A PROCR group undergoing a seven-day pre-trial creatine loading protocol (20g/day for 7 days) followed by 12 weeks of PRT with Cr (5g/day) and protein (30g/day) supplementation and a placebo (PLA) group undergoing a seven-day pre-trial placebo ingestion protocol followed by an identical PRT protocol with placebo supplementation. LBM increased non-significantly (1.3 kg) in the PLA group and increased significantly (2.6 kg) in the PROCR group. Though there were no statistically significant differences between groups at 12 weeks, given the dramatic losses of LBM seen in this patient population, the numerical two-fold (but not statistically signifcant) increase in LBM difference between groups should be viewed as having potentially large clinical significance. Though speculative, given that both groups consumed similar amounts of protein (as reported by mean values across the intervention) throughout the study (despite supplementation in the PROCR group), the Cr in the PROCR may have contributed to the additional LBM accrued in the PROCR group.

6.The potential therapeutic role of Cr Supplementation to treat cancer-related physical impairments.

The combination of cardiovascular, musculoskeletal, and neurological impairments experienced by individuals with cancer, coupled with cancer-related fatigue, can result in deleterious effects on physical function.[92] Indeed, individuals with cancer can often present with low physical function

status at the onset of treatment, or experience severe deterioration over the course of treatment.[111-113] Reductions in performance measures such as gait speed, stair climbing ability and timed up and go are regularly seen amongst cancer patients and survivors, particularly when compared to apparently healthy controls.[114-116] Undoubtedly, these decrements in physical function are inextricably linked to the decline of force-generating capabilities of skeletal muscle.

Impairments in muscle strength and an increase in fatigability are regularly reported in patients following cancer treatment.[115] Burden et al.[117] found that in a sample of 87 early-stage colorectal patients, about half (54%) had a handgrip strength <85% below the reference range.[118] Advanced prostate cancer patients undergoing ADT have shown 29% lower handgrip strength compared to healthy controls. Further, breast cancer survivors have displayed lower muscle strength (20-30%) in multiple upper body exercises compared with healthy individuals.[119] The clinical implications of these reductions in muscle strength and physical function in individuals with cancer are of critical importance, as those with lower levels of physical function are more likely to experience premature mortality than those with higher physical function.[92-94] Galvao et al.[120] proposed a theoretical model of the role of PRT to improve musculoskeletal fitness, resulting in an increase in physical reserve capacity in men treated with ADT. Here, we propose that Cr supplementation in addition to PRT may provide even more improvements in musculoskeletal fitness, results in a greater increase in physical reserve capacity (Figure 2). The changes have important implications in preserving physical function with age, and reducing the risk of falls and fractures amongst individuals with cancer.

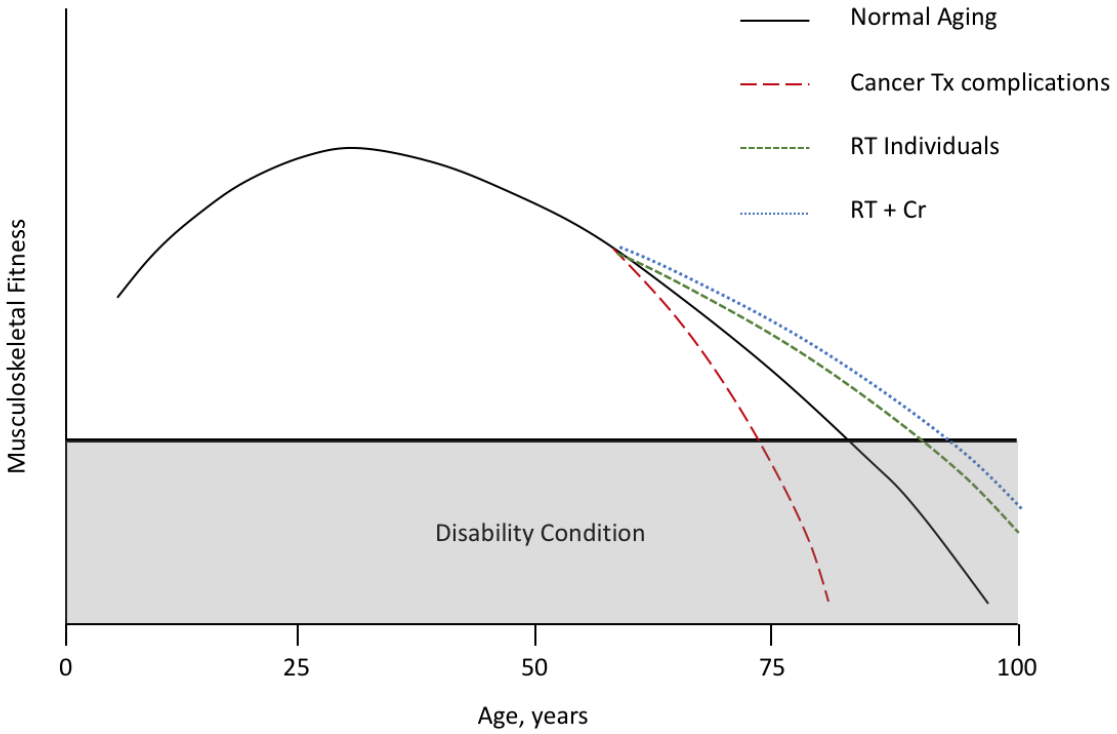

Figure 2. Theoretical model of the role of RT and Cr to attenuate musculoskeletal fitness decline in individuals with cancer.(Modified from Galvao et al. Prostate Cancer Prostatic Dis 2008) Certain cancer therapies can exacerbate declines in muscle mass and strength, leading to an accelerated decline in physical function toward a "disability" condition, or lack of independence. It has been proposed that PRT may delay this decline through increases in muscle mass, strength and functional ability. Here, we suggest that Cr supplementation in addition to PRT may lead to further improvements, potentially delaying this decline even longer. (print in color)

To date, only one trial has investigated the effects of Cr supplementation on physical function in individuals with cancer. The results of the DAHANCA 25A trial [23] in head and neck cancer patients that received radiotherapy, demonstrated that PRT increased muscle strength and functional performance with no additive effect of protein and Cr supplementation on physical function. However, the authors urged caution in interpretation of the results due to the low number of participants, minimal supervision during the training sessions, and adherence to the supplement only being reported using a questionnaire.

While the physiological mechanisms linking Cr supplementation to an increase in exercise performance are yet to be fully elucidated, one possibility is an increase in PCr content in Type II muscle fibers. PCr content is 5-15% higher in Type II than Type I fibers.[121, 122] Additionally, the rate of PCr degradation is faster in Type II than Type I fibers during high-intensity, short duration activities.[121] Conversely, Type I fibers resynthesise PCr at a faster rate than Type II fibers during recovery periods. After Cr supplementation, both fiber types increase total and PCr content, with a trend toward a larger increase in Type II fibers.[123] Type II muscle fibers are associated with higher anaerobic ATP turnover rate and peak power output during exercise. Evidence suggests that fatigue during intense muscle contraction may be attributable to the utilization of PCr, specifically in Type II muscle fibers.[124] Therefore, any mechanism capable of increasing intramuscular Cr stores may help to prevent PCr depletion, and delay fatigue, during intense exercise.

Earlier work by Harris et al.[32] showed increases in skeletal muscle Cr content by 20-50% following Cr supplementation, with 20% of the increase in Cr accounted for by increases in PCr. Although it is unclear whether or not cancer patients experience a significant decrease in PCr stores, there is evidence in clinical populations with muscle atrophy demonstrating depletion of intramuscular stores of PCr in Type II muscle fibers.[125] Therefore, while further research is needed in individuals with cancer, results from other clinical populations and muscle wasting diseases suggest it is plausible that Cr supplementation may have beneficial effects on muscle function and performance in this patient population.

7.Which cancer groups are most likely to benefit from Cr supplementation

The heterogeneity of cancer type, treatments, definitions of sarcopenia and cachexia, along with methods of assessment, makes it difficult to accurately define the prevalence of muscle wasting in cancer. Pamoukdjian et al.[72] indicated that patients with local oesophageal cancer and small-cell lung cancer represented the highest prevalence of pre-therapeutic sarcopenia, with respective values of 75% and 79.2%. In a study of 390 cancer patients, Sun et al.[126] found the highest prevalence of cachexia in pancreatic cancer (98.9%), gastric cancer (76.5%) and esophageal cancer (52.9%). Geriatric cancer patients are particularly vulnerable, given the already low muscle mass in this population. Indeed, Prado et al.[127] found 68% of cancer patients with sarcopenia were over the age of 65. Additionally, certain cancer treatments can result in muscle loss and dysfunction, such as ADT for prostate cancer.[88]

Certainly, given the results of studies in healthy aging and other clinical populations, any individual with cancer engaging in resistance training stands to benefit from Cr supplementation. Nevertheless, there may be subsets of cancer types, or treatments that may see greater benefit with Cr supplementation. Indeed, the highest prevalence of weight loss and cachexia has been observed in head and neck, pancreatic, lung, colorectal and gastric cancer.[3, 127] Older adults may be particularly vulnerable to muscle loss and could potentially benefit from Cr supplementation. Additionally, those undergoing certain treatments such ADT for prostate cancer are at a higher risk for muscle loss indicating the potential utility of Cr supplementation.

8.Safety considerations

Despite the expansive research supporting Cr as a safe and highly effective nutritional supplement in healthy aging and individuals with neurological/muscle disorders,[25, 33] it remains largely misunderstood, with unsubstantiated claims of side effects such as kidney and liver damage and dehydration. Contrary to these claims, Cr supplementation has not been associated with any signs of renal impairment.[25, 33, 128] Indeed, the safety of Cr supplementation on kidney function as measured by glomerular filtration rate has been demonstrated in a variety of apparently healthy and clinical populations.[129-132] In fact, Cr supplementation is being considered as a means to improve musculoskeletal and neurological functioning in patients with chronic kidney disease.[27] Long-term Cr supplementation has been investigated in other clinical populations such as Parkinson's disease and Huntington's disease, in studies ranging from 2-5 years, and doses up to 10g/day, with no adverse effects of supplementation or impact on renal dysfunction reported. [133-135]

Further, studies of Cr supplementation have reported no adverse effects on hydration status or muscle cramps. Researchers have conducted a meta-analysis and reported no evidence of altered hydration status or thermoregulation following Cr supplementation.[136] Additionally, Greenwood et al [137] found no increase in dehydration, cramping, and/or muscle injury rates among college football players following long-term (3 years) Cr supplementation. Cr is one of the most rigorously studied supplements to date, with hundreds of studies demonstrating safety, tolerability, and wide ranging health and performance benefits.[25, 33] Moreover, there is no compelling evidence that short- or long-term Cr supplementation has any detrimental effects on kidney function, gastrointestinal distress, muscle dysfunction or hydration status.[25, 33, 129-132]

It should be noted however, that given the paucity of research examining Cr supplementation in patients with cancer, studies examining the safety and tolerability of Cr in a cancer context, in particular interactions with treatments such as radiation therapy, chemotherapy, steroid therapy and immunotherapy, are necessary.

9.Conclusions and future directions

Given the beneficial effects of Cr supplementation on muscle mass, strength, BMD and physical function in a variety of clinical populations, the therapeutic potential for application in cancer is substantial. Indeed, randomized controlled trials are beginning to emerge, investigating the effects of Cr supplementation to attenuate cancer-related weight loss.[28] Nevertheless, application in various cancer contexts is still largely theoretical, with research in this area remaining sparse. Consequently, additional RCT's are needed in this area to fully understand the impact of supplementation on clinically-meaningful outcomes in individuals with cancer, in particular those at a higher risk of muscle wasting, such as head and neck, pancreatic, and gastrointestinal cancers.

The majority of studies in this area have examined Cr supplementation in isolation on clinical outcomes in individuals with cancer. Importantly, the beneficial effects of Cr supplementation are more likely a result of an increase in intramuscular Cr stores allowing an individual to get a greater "dose" of exercise, which can accumulate over time, leading to greater adaptations to exercise training (such as muscle mass, strength and physical function), than of the supplement alone. Accordingly, we recommend that future studies examine the effects of Cr supplementation in conjunction with resistance exercise on important clinical outcomes in individuals with cancer at a heightened risk of muscle loss (as mentioned above), such as muscle mass, strength and physical

function. Additionally, experiments in vitro or with animals are warranted to determine the mechanisms of effects of Cr to treat skeletal muscle toxicity in individuals with cancer. Collectively, further research in this area will allow for a greater understanding of the therapeutic effects of Cr supplementation in this patient population.

Conflict of interest statement
The authors declare that they have no conflict of interest.

Vitae

Dr. Ciaran Fairman

Dr. Ciaran Fairman, PhD, CSCS, ACSM-CET, is a Post-Doctoral Research Fellow at. the Exercise Medicine Research Institute. His research focuses on the different responses to exercise in cancer patients and survivors. He has served on several NIH-funded investigations (with funding exceeding $4 million) examining the effects of cognitive-behavioural exercise and dietary interventions on physical and psychosocial outcomes in clinical populations. He is currently co-investigator of an international research project (GAP4) investigating the impact of exercise medicine on progression free survival of men with advanced prostate cancer and a study coordinator of a recent NHMRC funded project of exercise in prostate cancer patients on active surveillance. Moreover, he is a co-investigator on several research projects in breast, prostate and head and neck cancer at US based Universities. He has published research in exercise oncology in some of the highest ranked-journals in the field.

Dr. Kristina Kendall

Kristina Kendall, Ph.D, CSCS*D, CISSN, EP-C is a lecturer in Exercise and Sports Sciences within the School of Medical and Health Sciences at Edith Cowan University. Her research areas and interests include examining physiological and performance adaptions to high-intensity interval training, dietary interventions to enhance the effects of physical activity, and the therapeutic effects of creatine monohydrate. Kristina has served as Co-PI, study coordinator, and co-investigator on several nutritional grants and contracts exceeding $600,000. More so, she has worked on several grants involving clinical populations, including elderly men and women, adolescents with cerebral palsy, and overweight/obese clients.

Dr. Nicolas Hart

Dr Nicolas Hart, PhD, AES, CSCS, ESSAM is a **Senior Research Fellow** for the Cancer Council of Western Australia at the Exercise Medicine Research Institute (an NHMRC Centre of Research Excellence) and an accredited exercise scientist, named 'WA Young Tall Poppy of the Year' (Australian Institute of Policy and Sciences, 2017) and 'Exercise Scientist of the Year' (Exercise and Sport Science Australia, 2014).

Dr Hart's clinical oncology work focuses on the ability of **exercise to change tumour biology, and attenuate tumour formation, growth and invasion in primary and secondary carcinomas**. He currently leads a series of world-first trials in humans, examining the suppressive and regressive effects of exercise on tumour morphology, tumour vasculature and tumour biomarkers in secondary carcinomas of advanced prostate and breast cancer patients with sclerotic and osteolytic bone metastatic lesions; with studies funded by Cancer Council of Western Australia, National Breast Cancer Foundation and Movember Foundation. Dr Hart is the *Global Exercise Coordinator*, and Co-Chair of the Protocol Amendment Review Committee for the Movember GAP4 (INTERVAL-MCRPC) trial - (the largest exercise trial in prostate cancer worldwide; investigating exercise and overall survival); and the *National Exercise Coordinator* for the Movember TrueNTH Australia trial - (the provision of local and remote delivery of exercise as medicine to prostate cancer patients across metropolitan and regional Australia).

Dr Hart is also a founding member of the Western Australian Bone Research Collaboration (WABRC): a cross-institutional and multidisciplinary team of researchers and clinicians investigating bone health and disease. Dr Hart continues to research in high performance sport, and is a consultant sport scientist to the West Coast Eagles (AFL), Fremantle Dockers (AFL), Western Force (Rugby Union) and Perth Glory (Soccer) sporting teams, providing input towards, and assisting in the prevention and management of stress-related bone injuries; stratify musculoskeletal injury risk; and provide a broad range of sport science services on request

Dr. Dennis Taaffe

Background

After initial teacher training Dennis completed his BSc, MSc, and PhD in the area of exercise physiology from the University of Oregon with postdoctoral training undertaken at Stanford University School of Medicine. Dennis has also received a DSc for work in exercise and ageing from Charles Sturt University and a MPH in Epidemiology from the University of Hawaii, is an Accredited Exercise Physiologist with Exercise and Sports Science Australia, a Fellow of the American College of Sports Medicine, and an Honorary Professor in the School of Human Movement and Nutrition Sciences at The University of Queensland. Prior to his recent appointment at ECU, Dennis was Professor and Discipline Leader for Medical and Exercise Science in the School of Medicine at the University of Wollongong, and Professor of Exercise Physiology and Program Convener for Exercise and Sport Science at the University of Newcastle.

Dr. Rob Newton

Biography

Professor Rob Newton is an Accredited Exercise Physiologist, Certified Strength and Conditioning Specialist with Distinction with the NSCA, Fellow of Exercise and Sports Science Australia and Fellow of the National Strength and Conditioning Association (NSCA). He has over 30 years of academic and professional experience in exercise and sports science and has been at ECU since 2003. Prior to appointment at ECU, Rob was Director of the Biomechanics Laboratory, at Ball State University in Indiana. He has also worked at the Pennsylvania State University as a visiting research fellow in the Center for Sports Medicine. Rob also holds an Adjunct Professorship at the University of Queensland and an Honorary Professorship at the University of Hong Kong. In 2004 he was awarded Outstanding Sports Scientist of the Year by the NSCA. He has published over 290 refereed scientific journal articles, two books, 16 book chapters and has a current h-Index of 59 with his work being cited over 12,500 times. As of 2016 his research had attracted over $29 Million in competitive research funding.

Rob has been a visiting researcher at the Centre for Sports Medicine, The Pennsylvania State University and was Director of the Biomechanics Laboratory at Ball State University. He has worked with numerous sporting organisations including New Jersey Nets, Chicago Bulls, Indianapolis Colts, Nike, England Rugby, Manchester United, Australian Institute of Sport, Fremantle Dockers FC, West Coast Eagles FC to name a few. He has served on several national and international committees and advisory boards including NHMRC Panels, ARC Excellence in Research for Australia, and Movember Global Prostate Cancer Survivorship Advisory Committee. Rob is an invited reviewer for 43 different scientific journals and is Senior Associate Editor for the Journal of Strength and Conditioning Research. He has supervised 29 PhD, 20 Masters and 3 Honours students to completion.

Dr. Daniel Galvão

Daniel Galvão is Professor of Exercise Science and Director of the Exercise Medicine Research Institute, Edith Cowan University, Perth, Western Australia, and a Cancer Council Western Australia Research Fellow. He received his B.Sc. (1998, Brazil) in Physical Education, M.Sc. (2003) in Clinical Exercise Science from the University of Queensland and his Ph.D. (2006) in Exercise Science from Edith Cowan University. Professor Galvão's research program focuses on applications of exercise as medicine for the prevention and management of cancer treatment side effects and survival and has received funding from NHMRC, Cancer Australia and the Prostate Cancer Foundation of Australia. His research has been published in the Journal of Clinical Oncology, European Urology and Nature Reviews Urology and he has co-authored the Exercise and Sports Science Australia position stand in exercise and cancer (2009) and the American College of Sports Medicine's exercise guidelines for cancer survivors (2010).

References

[1] Christensen JF, Jones LW, Andersen JL, Daugaard G, Rorth M, Hojman P. Muscle dysfunction in cancer patients. *Ann Oncol*. 2014;25(5):947-958. doi:10.1093/annonc/mdt551.

[2] Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *Eur J Cancer*. 2016;57:58-67. doi:10.1016/j.ejca.2015.12.030.

[3] Peterson SJ, Mozer M. Differentiating sarcopenia and cachexia among patients with cancer. *Nutr Clin Pract*. 2017;32(1):30-39. doi:10.1177/0884533616680354.

[4] Zhang G, Li X, Sui C, et al. Incidence and risk factor analysis for sarcopenia in patients with cancer. *Oncol Lett*. 2016;11(2):1230-1234. doi:10.3892/ol.2015.4019.

[5] Aversa Z, Costelli P, Muscaritoli M. Cancer-induced muscle wasting: latest findings in prevention and treatment. *Ther Adv Med Oncol*. 2017;9(5):369-382. doi:10.1177/1758834017698643.

[6] Barreto R, Mandili G, Witzmann FA, Novelli F, Zimmers TA, Bonetto A. Cancer and chemotherapy contribute to muscle loss by activating common signaling pathways. *Front Physiol*. 2016;7:472. doi:10.3389/fphys.2016.00472.

[7] Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409-1426. doi:10.1249/MSS.0b013e3181e0c112.

[8] Schmitz KH, Troxel AB, Cheville A, et al. Physical activity and lymphedema (the PAL trial): Assessing the safety of progressive strength training in breast cancer survivors. *Contemporary Clinical Trials*. 2009;30(3):233-245. doi:10.1016/j.cct.2009.01.001.

[9] 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(8):677-685. doi:10.1136/bjsports-2016-096537.

[10] Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*. 2010;28(2):340-347. doi:10.1200/JCO.2009.23.2488.

[11] Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*. 2007;25(28):4396-4404. doi:10.1200/JCO.2006.08.2024.

[12] van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-Intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. *J Clin Oncol*. 2015;33(17):1918-1927. doi:10.1200/JCO.2014.59.1081.

[13] Travier N, Velthuis MJ, Steins Bisschop CN, et al. Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial. *BMC Med*. 2015;13(1):121. doi:10.1186/s12916-015-0362-z.

[14] Thomas GA, Cartmel B, Harrigan M, et al. The effect of exercise on body composition and bone mineral density in breast cancer survivors taking aromatase inhibitors. *Obesity (Silver Spring)*. 2017;25(2):346-351. doi:10.1002/oby.21729.

[15] Nilsen TS, Raastad T, Skovlund E, et al. Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. *Acta Oncol*. 2015;54(10):1805-1813. doi:10.3109/0284186X.2015.1037008.

[16] Courneya KS, McKenzie DC, Mackey JR, et al. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst*. 2013;105(23):1821-1832. doi:10.1093/jnci/djt297.

[17] Gualano B, Artioli GG, Poortmans JR, Lancha Junior AH. Exploring the therapeutic role of creatine supplementation. *Amino Acids*. 2010;38(1):31-44. doi:10.1007/s00726-009-0263-6.

[18] Shachar SS, Deal AM, Weinberg M, et al. Body Composition as a predictor of toxicity in patients receiving anthracycline and taxane-based chemotherapy for early-stage breast cancer. *Clinical Cancer Research*. 2017;23(14):3537-3543. doi:10.1158/1078-0432.CCR-16-2266.

[19] Shachar SS, Deal AM, Weinberg M, et al. Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving taxane-based chemotherapy. *Clinical Cancer Research*. 2017;23(3):658-665. doi:10.1158/1078-0432.CCR-16-0940.

[20] Prado CMM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clinical Cancer Research*. 2009;15(8):2920-2926. doi:10.1158/1078-0432.CCR-08-2242

[21] de Campos-Ferraz PL, Andrade I, Neves das W, Hangai I, Alves CRR, Lancha AH. An overview of amines as nutritional supplements to counteract cancer cachexia. *J Cachexia Sarcopenia Muscle*. 2014;5(2):105-110. doi:10.1007/s13539-014-0138-x.

[22] Murphy RA, Mourtzakis M, Chu QSC, Baracos VE, Reiman T, Mazurak VC. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. *Cancer*. 2011;117(8):1775-1782. doi:10.1002/cncr.25709.

[23] Lønbro S, Dalgas U, Primdahl H, Overgaard J, Overgaard K. Feasibility and efficacy of progressive resistance training and dietary supplements in radiotherapy treated head and neck cancer patients--the DAHANCA 25A study. *Acta Oncol*. 2013;52(2):310-318. doi:10.3109/0284186X.2012.741325.

[24] Madzima TA, Ormsbee MJ, Schleicher EA, Moffatt RJ, Panton LB. Effects of resistance training and protein supplementation in breast cancer survivors. *Med Sci Sports Exerc*. 2017;49(7):1283-1292. doi:10.1249/MSS.0000000000001250.

[25] Kreider RB, Kalman DS, Antonio J, et al. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *J Int Soc Sports Nutr*. 2017;14(1):18. doi:10.1186/s12970-017-0173-z.

[26] Gualano B, de Salles Painelli V, Roschel H, et al. Creatine supplementation does not impair kidney function in type 2 diabetic patients: a randomized, double-blind, placebo-controlled, clinical trial. *Eur J Appl Physiol*. 2010;111(5):749-756. doi:10.1007/s00421-010-1676-3.

[27] Wallimann T, Riek U, Möddel M. Intradialytic creatine supplementation: A scientific rationale for improving the health and quality of life of dialysis patients. *Med Hypotheses*. 2017;99:1-14. doi:10.1016/j.mehy.2016.12.002.

[28] Jatoi A, Steen PD, Atherton PJ, et al. A double-blind, placebo-controlled randomized trial of creatine for the cancer anorexia/weight loss syndrome (N02C4): an Alliance trial. *Ann Oncol*. 2017;28(8):1957-1963. doi:10.1093/annonc/mdx232.

[29] Persky AM, Brazeau GA, Hochhaus G. Pharmacokinetics of the dietary supplement creatine. *Clin Pharmacokinet*. 2003;42(6):557-574. doi:10.2165/00003088-200342060-00005.

[30] Riesberg LA, Weed SA, McDonald TL, Eckerson JM, Drescher KM. Beyond muscles: The untapped potential of creatine. *Int Immunopharmacol*. 2016;37:31-42. doi:10.1016/j.intimp.2015.12.034.

[31] Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger HM. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the “phosphocreatine circuit” for cellular energy homeostasis. *Biochem J*. 1992;281 (Pt 1)(Pt 1):21-40.

[32] Harris RC, Söderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin Sci*. 1992;83(3):367-374.

[33] Buford TW, Kreider RB, Stout JR, et al. International Society of Sports Nutrition position stand: creatine supplementation and exercise. *J Int Soc Sports Nutr*. 2007;4(1):6. doi:10.1186/1550-2783-4-6.

[34] Olsen S, Aagaard P, Kadi F, et al. Creatine supplementation augments the increase in satellite cell and myonuclei number in human skeletal muscle induced by strength training. *J Physiol (Lond)*. 2006;573(Pt 2):525-534. doi:10.1113/jphysiol.2006.107359.

[35] Rawson ES, Venezia AC. Use of creatine in the elderly and evidence for effects on cognitive function in young and old. *Amino Acids*. 2011;40(5):1349-1362. doi:10.1007/s00726-011-0855-9.

[36] Chilibeck PD, Kaviani M, Candow DG, Zello GA. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. *Open Access J Sports Med*. 2017;8:213-226. doi:10.2147/OAJSM.S123529.

[37] Devries MC, Phillips SM. Creatine supplementation during resistance training in older adults-a meta-analysis. *Med Sci Sports Exerc*. 2014;46(6):1194-1203. doi:10.1249/MSS.0000000000000220.

[38] Smith RN, Agharkar AS, Gonzales EB. A review of creatine supplementation in age-related diseases: more than a supplement for athletes. *F1000Res*. 2014;3:222. doi:10.12688/f1000research.5218.1.

[39] Kley RA, Tarnopolsky MA, Vorgerd M. Creatine for treating muscle disorders. Cochrane Neuromuscular Group, ed. *Cochrane Database Syst Rev*. 2013;28(6):CD004760. doi:10.1002/14651858.CD004760.pub4.

[40] Campbell WW, Barton ML, Cyr-Campbell D, et al. Effects of an omnivorous diet compared with a lactoovovegetarian diet on resistance-training-induced changes in body composition and skeletal muscle in older men. *Am J Clin Nutr*. 1999;70(6):1032-1039. doi:10.1093/ajcn/70.6.1032.

[41] Smith SA, Montain SJ, Matott RP, Zientara GP, Jolesz FA, Fielding RA. Creatine supplementation and age influence muscle metabolism during exercise. *J Appl Physiol*. 1998;85(4):1349-1356. doi:10.1152/jappl.1998.85.4.1349.

[42] Stout JR, Sue Graves B, Cramer JT, et al. Effects of creatine supplementation on the onset of neuromuscular fatigue threshold and muscle strength in elderly men and women (64 - 86 years). *J Nutr Health Aging*. 2007;11(6):459-464.

[43] Gotshalk LA, Kraemer WJ, Mendonca MAG, et al. Creatine supplementation improves muscular performance in older women. *Eur J Appl Physiol*. 2008;102(2):223-231. doi:10.1007/s00421-007-0580-y.

[44] Cañete S, San Juan AF, Pérez M, et al. Does creatine supplementation improve functional capacity in elderly women? *Journal of Strength and Conditioning Research*. 2006;20(1):22-28. doi:10.1519/R-17044.1.

[45] Gotshalk LA, Volek JS, Staron RS, Denegar CR, Hagerman FC, Kraemer WJ. Creatine supplementation improves muscular performance in older men. *Med Sci Sports Exerc*. 2002;34(3):537-543.

[46] Brose A, Parise G, Tarnopolsky MA. Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. *J Gerontol A Biol Sci Med Sci*. 2003;58(1):11-19.

[47] Gualano B, Macedo AR, Alves CRR, et al. Creatine supplementation and resistance training in vulnerable older women: a randomized double-blind placebo-controlled clinical trial. *Exp Gerontol*. 2014;53:7-15. doi:10.1016/j.exger.2014.02.003.

[48] Candow DG, Little JP, Chilibeck PD, et al. Low-dose creatine combined with protein during resistance training in older men. *Med Sci Sports Exerc*. 2008;40(9):1645-1652. doi:10.1249/MSS.0b013e318176b310.

[49] Chilibeck PD, Chrusch MJ, Chad KE, Shawn Davison K, Burke DG. Creatine monohydrate and resistance training increase bone mineral content and density in older men. *J Nutr Health Aging*. 2005;9(5):352-353.

[50] Duff WRD, Kontulainen SA, Candow DG, et al. Effects of low-dose ibuprofen supplementation and resistance training on bone and muscle in postmenopausal women: A randomized controlled trial. *Bone Rep*. 2016;5:96-103. doi:10.1016/j.bonr.2016.04.004.

[51] Chilibeck PD, Candow DG, Landeryou T, Kaviani M, Paus-Jenssen L. Effects of creatine and resistance training on bone health in postmenopausal women. *Med Sci Sports Exerc*. 2015;47(8):1587-1595. doi:10.1249/MSS.0000000000000571.

[52] Lobo DM, Tritto AC, da Silva LR, et al. Effects of long-term low-dose dietary creatine supplementation in older women. *Exp Gerontol*. 2015;70:97-104. doi:10.1016/j.exger.2015.07.012.

[53] Andrews R, Greenhaff P, Curtis S, Perry A, Cowley AJ. The effect of dietary creatine supplementation on skeletal muscle metabolism in congestive heart failure. *Eur Heart J*. 1998;19(4):617-622.

[54] Louis M, Lebacq J, Poortmans JR, et al. Beneficial effects of creatine supplementation in dystrophic patients. *Muscle Nerve*. 2003;27(5):604-610. doi:10.1002/mus.10355.

[55] Tarnopolsky MA, Mahoney DJ, Vajsar J, et al. Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. *Neurology*. 2004;62(10):1771-1777.

[56] Sakkas GK, Mulligan K, Dasilva M, et al. Creatine fails to augment the benefits from resistance training in patients with HIV infection: a randomized, double-blind, placebo-controlled study. *PLoS ONE*. 2009;4(2):e4605. doi:10.1371/journal.pone.0004605.

[57] Coats AJS. Origin of symptoms in patients with cachexia with special reference to weakness and shortness of breath. *Int J Cardiol*. 2002;85(1):133-139.

[58] Lipkin DP, Jones DA, Round JM, Poole-Wilson PA. Abnormalities of skeletal muscle in patients with chronic heart failure. *Int J Cardiol*. 1988;18(2):187-195.

[59] Wiener DH, Fink LI, Maris J, Jones RA, Chance B, Wilson JR. Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow. *Circulation*. 1986;73(6):1127-1136.

[60] Broqvist M, Dahlström U, Karlsson E, Larsson J. Muscle energy metabolism in severe chronic congestive heart failure--effect of treatment with enalapril. *Eur Heart J*. 1992;13(9):1217-1224.

[61] Mancini DM, Ferraro N, Tuchler M, Chance B, Wilson JR. Detection of abnormal calf muscle metabolism in patients with heart failure using phosphorus-31 nuclear magnetic resonance. *Am J Cardiol*. 1988;62(17):1234-1240.

[62] Kley RA, Vorgerd M, Tarnopolsky MA. Creatine for treating muscle disorders. Kley RA, ed. *Cochrane Database Syst Rev*. 2007;58(1):CD004760. doi:10.1002/14651858.CD004760.pub2.

[63] Collins J, Noble S, Chester J, Coles B, Byrne A. The assessment and impact of sarcopenia in lung cancer: a systematic literature review. *BMJ Open*. 2014;4(1):e003697. doi:10.1136/bmjopen-2013-003697.

[64] Miyamoto Y, Baba Y, Sakamoto Y, et al. Negative impact of skeletal muscle loss after systemic chemotherapy in patients with unresectable colorectal cancer. *PLoS ONE*. 2015;10(6):e0129742. doi:10.1371/journal.pone.0129742.

[65] Ishii N, Iwata Y, Nishikawa H, et al. Effect of pretreatment psoas muscle mass on survival for patients with unresectable pancreatic cancer undergoing systemic chemotherapy. *Oncol Lett*. 2017;14(5):6059-6065. doi:10.3892/ol.2017.6952.

[66] Choi Y, Oh D-Y, Kim T-Y, et al. Skeletal muscle depletion predicts the prognosis of patients with advanced pancreatic cancer undergoing palliative chemotherapy, independent of body mass index. *PLoS ONE*. 2015;10(10):e0139749. doi:10.1371/journal.pone.0139749.

[67] Gu W, Wu J, Liu X, et al. Early skeletal muscle loss during target therapy is a prognostic biomarker in metastatic renal cell carcinoma patients. *Sci Rep*. 2017;7(1):7587. doi:10.1038/s41598-017-07955-6.

[68] Larsson L. Histochemical characteristics of human skeletal muscle during aging. *Acta Physiol Scand*. 1983;117(3):469-471. doi:10.1111/j.1748-1716.1983.tb00024.x.

[69] McKenna CF, Fry CS. Altered satellite cell dynamics accompany skeletal muscle atrophy during chronic illness, disuse, and aging. *Curr Opin Clin Nutr Metab Care*. 2017;20(6):447-452. doi:10.1097/MCO.0000000000000409.

[70] Marty E, Liu Y, Samuel A, Or O, Lane J. A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease. *Bone*. 2017;105:276-286. doi:10.1016/j.bone.2017.09.008.

[71] Paireder M, Asari R, Kristo I, et al. Impact of sarcopenia on outcome in patients with esophageal resection following neoadjuvant chemotherapy for esophageal cancer. *Eur J Surg Oncol*. 2017;43(2):478-484. doi:10.1016/j.ejso.2016.11.015.

[72] Pamoukdjian F, Bouillet T, Lévy V, Soussan M, Zelek L, Paillaud E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. *Clin Nutr*. July 2017. doi:10.1016/j.clnu.2017.07.010.

[73] Huang D-D, Wang S-L, Zhuang C-L, et al. Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. *Colorectal Dis*. 2015;17(11):O256-O264. doi:10.1111/codi.13067.

[74] Wang S-L, Zhuang C-L, Huang D-D, et al. Sarcopenia Adversely Impacts Postoperative Clinical Outcomes Following Gastrectomy in Patients with Gastric Cancer: A Prospective Study. *Ann Surg Oncol*. 2015;23(2):556-564. doi:10.1245/s10434-015-4887-3.

[75] S Morishita S, Kaida K, Tanaka T, et al. Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. *Support Care Cancer*. 2012;20(12):3161-3168. doi:10.1007/s00520-012-1460-5.

[76] Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489-495. doi:10.1016/S1470-2045(10)70218-7.

[77] Bruggeman AR, Kamal AH, LeBlanc TW, Ma JD, Baracos VE, Roeland EJ. Cancer cachexia: beyond weight loss. *J Oncol Pract*. 2016;12(11):1163-1171. doi:10.1200/JOP.2016.016832.

[78] Tisdale MJ. Mechanisms of cancer cachexia. *Physiol Rev*. 2009;89(2):381-410. doi:10.1152/physrev.00016.2008.

[79] Aoyagi T, Terracina KP, Raza A, Matsubara H, Takabe K. Cancer cachexia, mechanism and treatment. *World J Gastrointest Oncol*. 2015;7(4):17-29. doi:10.4251/wjgo.v7.i4.17.

[80] Penet M-F, Bhujwalla ZM. Cancer cachexia, recent advances, and future directions. *Cancer J*. 2015;21(2):117-122. doi:10.1097/PPO.0000000000000100.

[81] Sheean PM, Hoskins K, Stolley M. Body composition changes in females treated for breast cancer: a review of the evidence. *Breast Cancer Res Treat*. 2012;135(3):663-680. doi:10.1007/s10549-012-2200-8.

[82] Cheney CL, Mahloch J, Freeny P. Computerized tomography assessment of women with weight changes associated with adjuvant treatment for breast cancer. *Am J Clin Nutr*. 1997;66(1):141-146.

[83] Demark-Wahnefried W, Peterson BL, Winer EP, et al. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol*. 2001;19(9):2381-2389. doi:10.1200/JCO.2001.19.9.2381.

[84] Campbell KL, Lane K, Martin AD, Gelmon KA, McKenzie DC. Resting energy expenditure and body mass changes in women during adjuvant chemotherapy for breast cancer. *Cancer Nursing*. 2007;30(2):95-100. doi:10.1097/01.NCC.0000265004.64440.5f.

[85] Gordon AM, Hurwitz S, Shapiro CL, Leboff MS. Premature ovarian failure and body composition changes with adjuvant chemotherapy for breast cancer. *Menopause*. 2011;18(11):1244-1248. doi:10.1097/gme.0b013e31821b849b.

[86] Freedman RJ, Aziz N, Albanes D, et al. Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. *J Clin Endocrinol Metab*. 2004;89(5):2248-2253. doi:10.1210/jc.2003-031874.

[87] Spry NA, Taaffe DR, England PJ, et al. Long-term effects of intermittent androgen suppression therapy on lean and fat mass: a 33-month prospective study. *Prostate Cancer Prostatic Dis*. 2013;16(1):67-72. doi:10.1038/pcan.2012.33.

[88] Galvão DA, Spry NA, Taaffe DR, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int*. 2008;102(1):44-47. doi:10.1111/j.1464-410X.2008.07539.x.

[89] Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab*. 2002;87(2):599-603. doi:10.1210/jcem.87.2.8299.

[90] Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9(1):30. doi:10.1186/1710-1492-9-30.

[91] Gualano B, Rawson ES, Candow DG, Chilibeck PD. Creatine supplementation in the aging population: effects on skeletal muscle, bone and brain. *Amino Acids*. 2016;48(8):1793-1805. doi:10.1007/s00726-016-2239-7.

[92] Brown JC, Harhay MO, Harhay MN. Physical function as a prognostic biomarker among cancer survivors. *British Journal of Cancer*. 2015;112(1):194-198. doi:10.1038/bjc.2014.568.

[93] Sehl M, Lu X, Silliman R, Ganz PA. Decline in physical functioning in first 2 years after breast cancer diagnosis predicts 10-year survival in older women. *J Cancer Surviv*. 2013;7(1):20-31. doi:10.1007/s11764-012-0239-5.

[94] Brown JC, Harhay MO, Harhay MN. Patient-reported versus objectively-measured physical function and mortality risk among cancer survivors. *J Geriatr Oncol*. 2016;7(2):108-115. doi:10.1016/j.jgo.2016.01.009.

[95] Deldicque L, Atherton P, Patel R, et al. Effects of resistance exercise with and without creatine supplementation on gene expression and cell signaling in human skeletal muscle. *J Appl Physiol*. 2008;104(2):371-378. doi:10.1152/japplphysiol.00873.2007.

[96] Safdar A, Yardley NJ, Snow R, Melov S, Tarnopolsky MA. Global and targeted gene expression and protein content in skeletal muscle of young men following short-term creatine monohydrate supplementation. *Physiol Genomics*. 2008;32(2):219-228. doi:10.1152/physiolgenomics.00157.2007.

[97] Willoughby DS, Rosene J. Effects of oral creatine and resistance training on myosin heavy chain expression. *Med Sci Sports Exerc*. 2001;33(10):1674-1681.

[98] Drake MT. Osteoporosis and cancer. *Curr Osteoporos Rep*. 2013;11(3):163-170. doi:10.1007/s11914-013-0154-3.

[99] Brown SA, Guise TA. Cancer-associated bone disease. *Curr Osteoporos Rep*. 2007;5(3):120-127.

[100] Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst*. 2005;97(1):59-69. doi:10.1093/jnci/dji002.

[101] Pore SK, Hahm E-R, Latoche JD, Anderson CJ, Shuai Y, Singh SV. Prevention of breast cancer-induced osteolytic bone resorption by benzyl isothiocyanate. *Carcinogenesis*. 2018;39(2):134-145. doi:10.1093/carcin/bgx114.

[102] Oh YL, Yoon MS, Suh DS, et al. Changes in bone density after cancer treatment in patients with cervical and endometrial cancer. *J Cancer*. 2015;6(1):82-89. doi:10.7150/jca.10679.

[103] Michaud LB, Goodin S. Cancer-treatment-induced bone loss, part 1. *Am J Health Syst Pharm*. 2006;63(5):419-430. doi:10.2146/ajhp050045.p1.

[104] Le Pape F, Vargas G, Clézardin P. The role of osteoclasts in breast cancer bone metastasis. *J Bone Oncol*. 2016;5(3):93-95. doi:10.1016/j.jbo.2016.02.008.

[105] Khan MN, Khan AA. Cancer treatment-related bone loss: a review and synthesis of the literature. *Curr Oncol*. 2008;15(Suppl 1):S30-S40.

[106] Hart NH, Nimphius S, Rantalainen T, Ireland A, Siafarikas A, Newton RU. Mechanical basis of bone strength: influence of bone material, bone structure and muscle action. *J Musculoskelet Neuronal Interact*. 2017;17(3):114-139.

[107] Antolic A, Roy BD, Tarnopolsky MA, et al. Creatine monohydrate increases bone mineral density in young Sprague-Dawley rats. *Med Sci Sports Exerc*. 2007;39(5):816-820. doi:10.1249/mss.0b013e318031fac4.

[108] Gerber I, ap Gwynn I, Alini M, Wallimann T. Stimulatory effects of creatine on metabolic activity, differentiation and mineralization of primary osteoblast-like cells in monolayer and micromass cell cultures. *Eur Cell Mater*. 2005;10:8-22.

[109] J Bourgeois JM, Nagel K, Pearce E, Wright M, Barr RD, Tarnopolsky MA. Creatine monohydrate attenuates body fat accumulation in children with acute lymphoblastic leukemia during maintenance chemotherapy. *Pediatr Blood Cancer*. 2008;51(2):183-187. doi:10.1002/pbc.21571.

[110] Norman K, Stübler D, Baier P, et al. Effects of creatine supplementation on nutritional status, muscle function and quality of life in patients with colorectal cancer--a double blind randomised controlled trial. *Clin Nutr*. 2006;25(4):596-605. doi:10.1016/j.clnu.2006.01.014.

[111] Levy ME, Perera S, van Londen GJ, Nelson JB, Clay CA, Greenspan SL. Physical function changes in prostate cancer patients on androgen deprivation therapy: a 2-year prospective study. *Urology*. 2008;71(4):735-739. doi:10.1016/j.urology.2007.09.018.

[112] Given B, Given C, Azzouz F, Stommel M. Physical functioning of elderly cancer patients prior to diagnosis and following initial treatment. *Nurs Res*. 2001;50(4):222-232.

[113] Silver HJ, Dietrich MS, Murphy BA. Changes in body mass, energy balance, physical function, and inflammatory state in patients with locally advanced head and neck cancer treated with concurrent chemoradiation after low-dose induction chemotherapy. *Head Neck*. 2007;29(10):893-900. doi:10.1002/hed.20607.

[114] Storer TW, Miciek R, Travison TG. Muscle function, physical performance and body composition changes in men with prostate cancer undergoing androgen deprivation therapy. *Asian J Androl*. 2012;14(2):204-221. doi:10.1038/aja.2011.104.

[115] Granger CL, McDonald CF, Irving L, et al. Low physical activity levels and functional decline in individuals with lung cancer. *Lung Cancer*. 2014;83(2):292-299. doi:10.1016/j.lungcan.2013.11.014.

[116] Gonzalez BD, Jim HSL, Small BJ, et al. Changes in physical functioning and muscle strength in men receiving androgen deprivation therapy for prostate cancer: a controlled comparison. *Support Care Cancer*. 2016;24(5):2201-2207. doi:10.1007/s00520-015-3016-y.

[117] Soyupek F, Soyupek S, Perk H, Ozorak A. Androgen deprivation therapy for prostate cancer: effects on hand function. *Urol Oncol*. 2008;26(2):141-146. doi:10.1016/j.urolonc.2006.12.014.

[118] Burden ST, Hill J, Shaffer JL, Todd C. Nutritional status of preoperative colorectal cancer patients. *J Hum Nutr Diet*. 2010;23(4):402-407. doi:10.1111/j.1365-277X.2010.01070.x.

[119] Harrington S, Padua D, Battaglini C, et al. Comparison of shoulder flexibility, strength, and function between breast cancer survivors and healthy participants. *J Cancer Surviv*. 2011;5(2):167-174. doi:10.1007/s11764-010-0168-0.

[120] Galvão DA, Taaffe DR, Spry N, Newton RU. Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. *Prostate Cancer Prostatic Dis*. 2007;10(4):340-346. doi:10.1038/sj.pcan.4500975.

[121] Greenhaff PL, Nevill ME, Söderlund K, et al. The metabolic responses of human type I and II muscle fibres during maximal treadmill sprinting. *J Physiol (Lond)*. 1994;478 (Pt 1):149-155. doi:10.1111/(ISSN)1469-7793.

[122] Söderlund K, Hultman E. ATP and phosphocreatine changes in single human muscle fibers after intense electrical stimulation. *Am J Physiol*. 1991;261(6 Pt 1):E737-E741. doi:10.1152/ajpendo.1991.261.6.E737.

[123] Casey A, Constantin-Teodosiu D, Howell S, Hultman E, Greenhaff PL. Creatine ingestion favorably affects performance and muscle metabolism during maximal exercise in humans. *Am J Physiol*. 1996;271(1 Pt 1):E31-E37. doi:10.1152/ajpendo.1996.271.1.E31.

[124] Hultman E, Greenhaff PL, Ren JM, Söderlund K. Energy metabolism and fatigue during intense muscle contraction. *Biochem Soc Trans*. 1991;19(2):347-353.

[125] Sipilä I, Rapola J, Simell O, Vannas A. Supplementary creatine as a treatment for gyrate atrophy of the choroid and retina. *N Engl J Med*. 1981;304(15):867-870. doi:10.1056/NEJM198104093041503.

[126] Sun L, Quan X-Q, Yu S. An epidemiological survey of cachexia in advanced cancer patients and analysis on its diagnostic and treatment status. *Nutr Cancer*. 2015;67(7):1056-1062. doi:10.1080/01635581.2015.1073753.

[127] Prado CMM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9(7):629-635. doi:10.1016/S1470-2045(08)70153-0.

[128] Bender A, Samtleben W, Elstner M, Klopstock T. Long-term creatine supplementation is safe in aged patients with Parkinson disease. *Nutr Res*. 2008;28(3):172-178. doi:10.1016/j.nutres.2008.01.001.

[129] Poortmans JR, Auquier H, Renaut V, Durussel A, Saugy M, Brisson GR. Effect of short-term creatine supplementation on renal responses in men. *Eur J Appl Physiol Occup Physiol*. 1997;76(6):566-567. doi:10.1007/s004210050291.

[130] Gualano B, Ugrinowitsch C, Novaes RB, et al. Effects of creatine supplementation on renal function: a randomized, double-blind, placebo-controlled clinical trial. *Eur J Appl Physiol*. 2008;103(1):33-40. doi:10.1007/s00421-007-0669-3.

[131] Neves M, Gualano B, Roschel H, et al. Effect of creatine supplementation on measured glomerular filtration rate in postmenopausal women. *Appl Physiol Nutr Metab*. 2011;36(3):419-422. doi:10.1139/h11-014.

[132] Lugaresi R, Leme M, de Salles Painelli V, et al. Does long-term creatine supplementation impair kidney function in resistance-trained individuals consuming a high-protein diet? *J Int Soc Sports Nutr*. 2013;10(1):26. doi:10.1186/1550-2783-10-26.

[133] Bender A, Klopstock T. Creatine for neuroprotection in neurodegenerative disease: end of story? *Amino Acids*. 2016;48(8):1929-1940. doi:10.1007/s00726-015-2165-0.

[134] Kieburtz K, Tilley BC, Elm JJ, et al. Effect of creatine monohydrate on clinical progression in patients with parkinson disease: A randomized clinical trial. *JAMA*. 2015;313(6):584-593. doi:10.1001/jama.2015.120.

[135] Bender A, Koch W, Elstner M, et al. Creatine supplementation in Parkinson disease: A placebo-controlled randomized pilot trial. *Neurology*. 2006;67(7):1262-1264. doi:10.1212/01.wnl.0000238518.34389.12.

[136] Lopez RM, Casa DJ, McDermott BP, Ganio MS, Armstrong LE, Maresh CM. Does creatine supplementation hinder exercise heat tolerance or hydration status? A systematic review with meta-analyses. *J Athl Train*. 2009;44(2):215-223. doi:10.4085/1062-6050-44.2.215.

[137] Greenwood M, Kreider RB, Melton C, et al. Creatine supplementation during college football training does not increase the incidence of cramping or injury. *Mol Cell Biochem*. 2003;244(1-2):83-88.

The authors declare that they have no conflict of interest.