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

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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 nutritional/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.

## 1. Introduction

Individuals with cancer are at a high risk of skeletal muscle wasting that may be exacerbated by tumour-related factors and cancer therapies (certain hormone and chemotherapies in particular) (Barreto et al., 2016; Vaughan et al., 2013; Aversa et al., 2017; Christensen et al., 2014; Shachar et al., 2016). An emerging body of literature supports the role of exercise as a means to ameliorate these treatment-related declines and improve clinically relevant outcomes in individuals with cancer (Schmitz et al., 2009; Galvao et al., 2010; Focht et al., 2018; Fairman et al., 2017a). 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 (Galvao et al., 2010; Courneya et al., 2007, 2013; Nilsen et al., 2015; van Waart et al., 2015; Travier et al., 2015; Thomas et al., 2017). 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 (Shachar et al., 2017b; Prado et al., 2009; Gualano et al., 2010; Kreider et al., 2017). 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 (Shachar et al., 2016, 2017a; Shachar et al., 2017b; Prado et al., 2009; Gualano et al., 2010).

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 (Kreider et al., 2017). 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, myasthenia gravis, amyotrophic lateral sclerosis, and Parkinson's disease (Gualano et al., 2010, 2011; Wallimann et al., 2017). 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 (Jatoi et al., 2017). 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) highlight select studies investigating the therapeutic use

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of Cr supplementation on lean body mass, muscle strength and function in cancer and other clinical populations; and (3) provide perspectives on the potential therapeutic role of Cr supplementation to treat cancer-related physical impairments.

## 2. Creatine metabolism

Cr is a naturally-occurring substance in the human body, synthesized endogenously in the kidneys, pancreas, and liver from the amino acids arginine, glycine, and methionine at a rate of ~1-2 g/day (Persky et al., 2003). Additionally, approximately 1 g of Cr can be consumed by individuals with a diet high in meat and fish (Riesberg et al., 2016). The majority of Cr (95%) is stored in skeletal muscle (as free creatine or phosphocreatine), with the rest found in the brain and testes (Kreider et al., 2017). The total Cr pool (PCr + free Cr) in skeletal muscle averages about 120 g for a 70 kg individual. However, the average human has the capacity to store up to 160 g of Cr via diet or supplementation (Kreider et al., 2017). 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 (Kreider et al., 2017; Riesberg et al., 2016). The magnitude of the increase in skeletal muscle Cr content depends on the levels of Cr in the muscle prior to supplementation. Those who have lower muscle Cr stores, such as those who eat little meat or fish, are more likely to experience an increase of 20–40%, whereas those with relatively high muscle stores may only increase by 10–20% (Kreider et al., 2017).

Cr is a component of the high-energy phosphate, phosphocreatine (PCr), which plays a critical role in rapid energy provision during skeletal muscle contraction (de Campos-Ferraz et al., 2014). Re-phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP) during and following exercise (Fig. 1) is reliant on the amount of PCr stored in the muscle (PCr + ADP ↔ Cr + ATP) (Kreider et al., 2017). 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 (Wallimann et al., 1992).

There are reports of Cr supplementation without exercise training on body composition and muscle function. Safdar and colleagues demonstrated a significant increase in FFM, total body water, and body mass following 10 days of Cr supplementation (20 g/day × 3 days, 5 g/day x 7 days) in healthy, young adults (Safdar et al., 2008). More so, Cr supplementation significantly upregulated the mRNA content of genes and protein content of kinases involved in protein and glycogen synthesis regulation, satellite cell proliferation and differentiation, and DNA replication and repair. In older adults, Cr supplementation without RT has been shown to enhance fatigue resistance. Some investigators have reported increased strength, while others have demonstrated improved performance of activities of daily living (ADL) (Gotshalk et al., 2008, 2002; Stout et al., 2007).

It is hypothesized that Cr uptake by skeletal muscle is modulated by muscle activity (Harris et al., 1992). 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 (Kreider et al., 2017; Buford et al., 2007). 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 (Harris et al., 1992; Olsen et al., 2006), enhancing exercise capacity, and leading to an increase in training quality and overall training volume (Kreider et al., 2017; Buford et al., 2007). 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.

Importantly, the safety and efficacy of PRT has been well established, across a variety of cancer types and treatments. The adaptations to PRT depend on the systematic manipulation of key training parameters such as intensity and volume. The nuances of resistance exercise prescription are outside of the scope of this review. For more information, readers are directed to several reviews in this area (Fairman et al., 2017a; Padilha et al., 2017; Cheema et al., 2014; Fairman et al., 2017b; Neil-Sztramko et al., 2017).

## 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, for a more comprehensive overview, readers are directed to many of the recent systematic reviews and/or meta-analyses on the effect of Cr supplementation on LBM, muscle strength and function, or cognitive function in healthy individuals (Avgerinos et al., 2018; Lanhers et al., 2015, 2017) and older adults (Chilibeck et al., 2017; Devries and Phillips, 2014; Forbes et al., 2018; Rawson and Venezia, 2011), and those with neurodegenerative (Smith et al., 2014) and muscular disorders (Kley et al., 2013), as well as those with chronic obstructive pulmonary disease (COPD) (Al-Ghimlas and Todd, 2010).

### 3.1. Healthy 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 (Campbell et al., 1999) and middle-aged adults (Smith et al., 1985) than younger individuals. However, individuals with low intramuscular total Cr concentrations show an

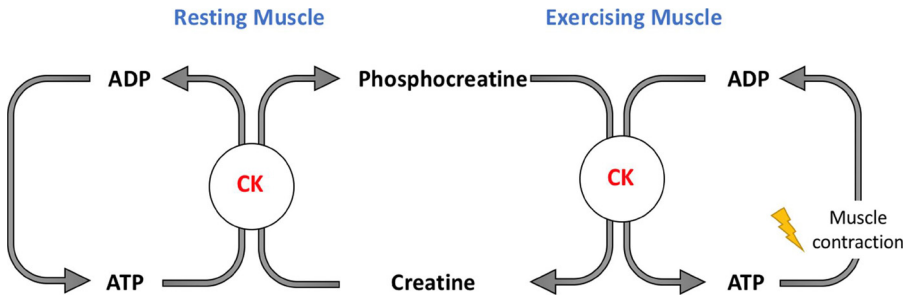


**Fig. 1.** Phosphocreatine shuttle system. Creatine catalyses reversible phosphorylation of creatine to Phosphocreatine and ADP to ATP. (print in colour).

**Table 1a**
Summary of select studies examining the effects of Cr supplementation on body composition, strength, and function in healthy aging/clinical populations with combined resistance training programs.

| Authors (year) | Participants (mean age ± SD) | Dosage | Protocol duration | Exercise program | Results | Adverse Effects related to supplementation |
|---|---|---|---|---|---|---|
| *Healthy Aging* | | | | | | |
| Aguiar et al. (2013) | 18 healthy women, (Cr: 64 ± 4 y; PLA: 65 ± 6 y) | 5 g/d for duration of study | 12 weeks | 3 x $wk^{-1}$, 10-15RM, 2 sets, WB training | ↑Upper and lower body strength, ↑FFM and muscle mass, ↔ BM or %BF | No adverse effects reported |
| Bemben et al. (2010) | 20 healthy adults, (Cr: 56.1 ± 1.8 y; PLA: 56.1 ± 1.4 y) | 7 g/ day 3 x $wk^{-1}$ for first 2 weeks, followed by 5 g/day | 14 weeks | 3 x $wk^{-1}$, 8 reps at 80% 1RM, 3 sets, WB training | ↔ Upper or lower body strength, ↔ LBM | No adverse effects reported |
| Bermon et al. (1998); | 16 healthy adults, (Cr: 71.0 ± 1.9 y; PLA: 69.3 ± 0.4 y) | 20 g/d for 5 days followed by 3 g/d | 8 weeks | 3 x $wk^{-1}$, 8 reps at 80% 1RM, 3 sets, leg press, knee extension, chest press | ↔ Upper or lower body strength | No adverse effects reported |
| Brose et al. (2003) | 28 older adults, (Men Cr: 68.7 ± 4.8 y, Females Cr: 70.8 ± 6.1 y; Men PLA 68.3 ± 3.2 y, Females PLA: 69.9 ± 5.6 y) | 5 g/d | 14 weeks | 3 x $wk^{-1}$, 10-12 reps at 80% 1RM, 3 sets, WB training | ↑ Total body mass; ↑ FFM; ↑ ISO knee ext. | No adverse effects reported |
| Candow et al. (2008) | 25 older men, (Cr: 65.5 ± 2.7 y; PLA: 64.1 ± 3.1 y) | 0.10 g/kg/d | 10 weeks | 3 x $wk^{-1}$, 10 reps at 80% 1RM, 3 sets, WB training | ↑ muscle thickness; ↔ Upper or lower body 1RM, ↓ 30% bone resorption, PLAA ↑ 13% bone resorption | No adverse effects reported |
| Chilibeck et al. (2015) | 33 healthy women, (Cr: 57 ± 4 y; PLA 57 ± 7 y) | 0.1 g/kg/d | 52 weeks | 3 x $wk^{-1}$, 10 reps at 80% 1RM, 3 sets, WB training | ↑ Upper body strength, ↔ in LBM or lower body strength | GI adverse effects, Cr = 5 vs PLA = 2; Muscle cramps, Cr = 2, no adverse events related to liver or kidney function. |
| Chilibeck et al. (2005) | 29 older men, (Cr: 70.8 ± 6.6 y; PLA: 71.5 ± 6.7 y) | 0.3 g/kg/d for 5 days, 0.07 g/kg/d for 79 days | 12 weeks | 3 x $wk^{-1}$, 10 reps at 80% 1RM, 3 sets, WB training | ↑Upper limb BMC. ↔Legs, trunk or WB BMC. | No adverse effects reported |
| Chrusch et al. (2001) | 30 healthy men, (Cr: 70.4 ± 1.6 y; PLA: 71.1 ± 1.8 y) | 0.3 g/kg/day for 5 days followed by 0.07 g/kg/day | 12 weeks | 3 x $wk^{-1}$, 10 reps at 50-75% 1RM, 3 sets, WB training | ↑LBM, ↑Lower body strength and endurance, ↔ Upper body strength and endurance | Cr during loading phase increased GI adverse events |
| Cooke et al. (2014) | 20 healthy men, (Cr: 61.4 ± 5.0 y; PLA: 60.7 ± 5.4 y) | 20 g/d for 7 days followed by 0.1 g/d on training days | 12 weeks | 3 x $wk^{-1}$, 10 reps at 75% 1RM, 3 sets, WB training | ↔ LBM, ↔ Upper or lower body strength, ↔ type I or type II muscle fibre area | No adverse effects reported |
| Gualano et al. (2014) | 30 "vulnerable" women, (Cr: 67.1 ± 5.6 y; PLA: 63.6 ± 3.6 y) | 20 g/d for 5 days followed by 5 g/d | 24 weeks | 3 x $wk^{-1}$, 8-12 RM, 3 sets, WB training | ↑LBM, ↔ fat mass, ↑ Upper body strength, ↔ Lower body strength leg press strength, ↔ timed up and go test, STS | No adverse effects reported |
| Pinto et al. (2016) | 27 healthy adults, (Cr: 67.4 ± 4.7 y; PLA: 67.1 ± 6.3 y) | 5 g/d for duration of study | 12 weeks | 3 x $wk^{-1}$, 13-15 RM, 3 sets, WB training | ↑ LBM, ↔ Upper or lower body strength | No adverse events reported |
| *Clinical Populations* | | | | | | |
| Cornelissen et al. (2010) | 70 patients with coronary artery disease or chronic heart failure, (Cr: 55.0 ± 9.5 y; PLA: 59.7 ± 6.7 y) | 5 g/d for duration of study | 12 weeks | 3 x $wk^{-1}$, 8-12 RM, 2-3 sets, WB training + 45 minutes aerobic exercise | ↔ ISO or isokinetic knee extension strength | No adverse effects reported |
| Hass et al. (2007) | 20 patients with idiopathic Parkinson's disease, (Cr: 62.2 ± 2.6 y; PLA: 62.8 ± 2.6 y) | 20 g/d for 5 days followed by 5 g/d | 12 weeks | 2 x $wk^{-1}$, 10 reps at 50-70% 1RM, 1 set, WB training | ↑ Upper body strength, ↑ chair rise performance, ↔ Lower body strength or endurance | No adverse effects reported |
| Sakkas et al. (2009) | Patients with HIV infection, (Cr: 44 ± 9 y; PLA: 44 ± 8 y) | 20 g/d for 5 days then 5 g/d | 12 weeks | 3 x $wk^{-1}$, 8 reps at 80% 1RM, 4 sets, WB training | ↑ LBM | No adverse effects reported |

%BF: body fat percentage; BM: body mass; 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; GI: gastrointestinal; 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.

**Table 1b**
Summary of select studies examining the effects of Cr supplementation on body composition, strength, and function in healthy aging/clinical populations without combined resistance training programs.

| Authors (year) | Patient/ subjects | Dosage | Protocol duration | Results | Adverse Effects related to supplementation |
|---|---|---|---|---|---|
| *Healthy Aging* | | | | | |
| Gotshalk et al. (2002) | 18 healthy men, (Cr: 65.4 ± 1.5 y; PLA: 65.7 ± 2.0 y) | 0.3 g/kg/d | 1 week | ↑ FFM, ↑ Upper and lower body strength, ↑ LBP, ↓ STS, ↓ TG. | No adverse effects reported |
| Gotshalk et al. (2008) | 30 healthy women (Cr: 63.3 ± 1.2 y; PLA: 63.0 ± 1.1 y) | 0.3 g/kg/d | 1 week | ↑ Upper and lower body 1RM, ↑ FFM, ↑ UBMP & LBMP, ↓ STS, ↓TG. | No adverse effects reported |
| Lobo et al. (2015) | 109 post-menopausal, osteopenic women (Cr: 58 ± 5 y; PLA: 58 ± 6 y) | 1 g/d | 52 weeks | ↔ Lumbar spine, total hip or WB BMD | No adverse effects reported |
| Rawson and Clarkson (2000) | 17 healthy males, (Cr: 65.0 ± 2.1 y; PLA: 65.8 ± 1.4 y) | 20 g/d | 5 days | ↔ isokinetic performance, ↔ ISO strength | No adverse effects reported |
| Rawson et al. (1999) | 20 healthy males, (Cr: 66.7 ± 1.9 y; PLA: 66.9 ± 2.2 y) | 20 g/d for 10 days, followed by 4 g/d for 20 days | 30 days | ↔ FFM, ↔ Upper body strength, ↔ leg fatigue | No adverse effects reported |
| Stout et al. (2007) | 15 older adults (74.5 ± 6.4 y) | 20 g/d for 7 days then 10 g/d | 2 weeks | ↑ GRIP and PWCFT, ↔ STS or BW | No adverse effects reported |
| *Clinical Populations* | | | | | |
| Andrews et al. (1998) | 20 patients with chronic heart failure (Cr: 64.9 ± 5.7 y; PLA: 62.0 ± 6.5 y) | 20 g/d | 5 days | ↑ contractions before fatigue at 75% MVC; ↓ lactate % ammonia at 75% MVC | No adverse effects reported |
| Louis et al. (2003) | 15 boys with MD (10.8 ± 2.8 y) | 3 g/d | 12 weeks | ↑MVC, TTE; ↑BMD, ↓ urinary excretion of cross-linked N-telopeptides of Type I collagen in ambulatory patients. | No adverse effects reported |
| Tarnopolsky et al. (2004) | 30 boys with MD (S: 10.0 ± 0.8 y; NS: 10.4 ± 0.8 y) | 0.10 g/kg/d | 16 weeks | ↑ handgrip strength, ↑ FFM, ↓ urinary excretion of cross-linked N-telopeptides of Type I collagen** ↔ GMS, FT | No adverse effects reported |
| Walter et al. (2000) | 36 patients with muscular dystrophy (Adults: 35 ± 15 y; Children: 10 ± 4 y) | 10.6 g/day for 10 days then 5.3 g/d for 46 days | 8 weeks | ↑ muscle strength, ↑ NSS | No adverse effects reported |

BMC: Bone mineral content; BMD: Bone mineral density; BW: Bodyweight; Cr: creatine supplementation; g: gram; KE: knee extension; kg: kilogram; 1RM: 1 repetition maximum; FFM: Fat free mass; FT: functional tasks; GMS: global muscle strength; GRIP: maximal isometric grip strength; ISO: isometric; LBM: lean body mass; LBP: lower body power; LBMP: lower body mean power; MD: muscular dystrophy; MVC: maximum voluntary contraction; NS: non(cortico)steroid; NSS: neuromuscular symptom score: PWCFT: physical working capacity at fatigue threshold; PLA: Placebo group; S: (cortico) steroid; STS: sit − to − stand test; TG: tandem gait test; TTE: time to exhaustion; UBMP: upper body mean power; WB: whole body; n/a: not applicable; ↑: increase; ↓: decrease; ↔: no change; **compared to Placebo.

enhanced ability to increase creatine content following Cr supplementation (Harris et al., 1992). 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 (Gotshalk et al., 2008; Stout et al., 2007). A summary of the studies discussed in this review examining Cr supplementation in healthy aging/clinical populations with or without resistance training are presented in Tables 1a and 1b, respectively.

Stout et al. (2007) 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. (2008) 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 (Gotshalk et al., 2002). Supporting these findings, Canete et al. (2006) 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 (Chilibeck et al., 2005, 2015; Duff et al., 2016). Results from a meta-analysis undertaken by Devries and Phillips (2014) indicated that Cr supplementation during PRT enhanced the gain in LBM, strength, and functional performance over PRT alone in older adults. Similarly, Brose et al. (2003) 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 36-week 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 (Gualano et al., 2014).

Cr supplementation combined with PRT also has beneficial effects on bone health. In older men, 10 weeks of Cr supplementation (0.1 g/kg) combined with a structured PRT completed 3 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 (Candow et al., 2008). These results support previous findings from Chilibeck et al. (2005), showing Cr supplementation (0.3 g/kg for 5 days, 0.07 g/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 39 weeks to detect changes (Chilibeck et al., 2015; Duff et al., 2016), 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. (2015) investigated the effects of long-term, low-dose Cr supplementation (1 g/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. (2014) 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. (2003) found no effect from Cr supplementation (5 g/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 supplementation appear to have a beneficial effect on LBM, muscle strength and physical function and bone health in older adults (Devries and Phillips, 2014). However, longer term studies (> 52 weeks) with rigorous methodology utilising higher training volume with Cr are warranted.

### 3.2. Clinical 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 (Coats, 2002), which has been associated with accelerated disease progression and increased morbidity. A 2009 study by Sakkas et al. (2009) found that 14 weeks of Cr supplementation (20 g/d for the first 5 days, followed by a maintenance dose of 4.8 g/day), combined with 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 (Lipkin et al., 1988; Wiener et al., 1986). 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 (Broqvist et al., 1992; Mancini et al., 1988). Andrews et al. (1998) 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 12-weeks of Cr supplementation (3 g/day) in boys with Duchenne and Becker muscular dystrophy (Louis et al., 2003). 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 has the potential to affect bone as PCr is used to resynthesize ATP through the creatine kinase reaction in bone cells (Wallimann and Hemmer, 1994). Cr added to cell culture medium has been shown to increase the metabolic activity of osteoblast cells involved in bone formation (Gerber et al., 2005). Although not directly measured in the current study, an increase in osteoblast cell activity stimulates the production of osteoprotegerin, a protein that can inhibit osteoclast cell differentiation, resulting in less bone resorption (Yasuda et al., 1998). 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 (Canete et al., 2006).

Tarnopolsky et al. (2004) investigated the effects of Cr supplementation (0.1 g/kg) in young boys with Duchenne muscular dystrophy for 16-weeks. 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. Furthermore, following Cr supplementation, a significant increase in handgrip strength and FFM (+0.7 kg) was observed. In addition, Kley et al. (2013) 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. Muscle dysfunction, body composition and bone health 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 tumour-related factors, cancer therapies (in particular certain hormone and chemotherapies), malnutrition, physical inactivity along with increasing age and comorbidities (Barreto et al., 2016; Vaughan et al., 2013; Aversa et al., 2017; Christensen et al., 2014; Shachar et al., 2016). Some of the mechanisms of muscle dysfunction in cancer are outlined in the following subsections.

### 4.1. Sarcopenia

Sarcopenia refers to the age-related loss of muscle mass and function that typically accelerates with advancing age (Peterson and Mozer, 2017). Characterized by changes in tissue quality, decreases in satellite cells, denervation and/or atrophy of type II muscle fibres 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 (McKenna and Fry, 2017; Larsson, 1983; Marty et al., 2017). There is no clear international consensus on diagnostic criteria for sarcopenia, however, the European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass (appendicular skeletal muscle mass/height$^2$: men $\sim$7.26 kg/m$^2$, women $\sim$5.5 kg/m$^2$) and low muscle function indicated by either strength (handgrip strength: men $<$ 30 kg, women $<$ 20 kg) and/or performance (gait speed $<$ 0.8 m/s) (Cruz-Jentoft et al., 2010). 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 (Peterson and Mozer, 2017). Nevertheless, prevalence of sarcopenia in individuals with cancer can range from 11 to 74% depending on the diagnostic criteria and methods of assessment (Paireder et al., 2017; Pamoukdjian et al., 2018; Morishita et al., 2012; Wang et al., 2016; Huang et al., 2015).

### 4.2. Cachexia

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 (Aoyagi et al., 2015; Penet and Bhujwalla, 2015; Fearon et al., 2011). 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 26-weeks (Fearon et al., 2011). 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 (2009) and (Aoyagi et al., 2015). Briefly, this severe muscle wasting syndrome is thought to be a result of a combination of factors, including systemic inflammation, tumour metabolism and tumour-mediated effects, along with malnutrition and physical inactivity (Fearon et al., 2011). 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 (Penet and Bhujwalla, 2015; Fearon et al., 2011).

To date, the primary focus of research around muscle toxicity in cancer 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 (Collins et al., 2014), colorectal cancer (Miyamoto et al., 2015), pancreatic cancer (Ishii et al., 2017; Choi et al., 2015) and renal cell carcinoma (Gu et al., 2017). Sarcopenia and cachexia are somewhat distinct in their aetiology, 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.

### 4.3. Body composition

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 (Campbell et al., 2007). 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 (Campbell et al., 2007; Cheney et al., 1997; Demark-Wahnefried et al., 2001; Freedman et al., 2004). Accumulation of fat mass and/or loss of muscle mass have been documented in prostate cancer patients undergoing androgen deprivation therapy (ADT) (Smith et al., 2002; Galvao et al., 2008; Spry et al., 2013). Moreover, the use of corticosteroids to manage cancer and treatment side effects is associated with weight gain and redistribution of body fat (Gu et al., 2017). Indeed, Cushingoid features (truncal obesity, dorsocervical and facial adiposity) can develop within the first 8-weeks of glucocorticoid therapy (Gu et al., 2017).

### 4.4. Bone 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 (Drake, 2013; Brown and Guise, 2007). 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 (Brown and Guise, 2007; Brown et al., 2005; Pore et al., 2018). 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 (Drake, 2013; Michaud and Goodin, 2006; Oh et al., 2015; Le Pape et al., 2016). Indeed, adverse changes in BMD coupled with a deterioration in bone quality and microarchitecture increases fracture risk due to heightened bone fragility (Drake, 2013; Michaud and Goodin, 2006; Khan and Khan, 2008; Hart et al., 2017). Emerging evidence suggests Cr monohydrate may positively affect bone physiology, possibly by increasing the activity of osteoblast-like cells involved in bone formation (Gerber et al., 2005; Antolic et al., 2007) and decreasing bone resorption. (Candow et al., 2008; Louis et al., 2003)

Ultimately, regardless of the mechanism, the loss of LBM and reductions in muscle strength and physical function remains of chief concern in certain cancers (the magnitude of impairments in LBM, muscle strength and physical function varies as a result of the type and stage of cancer, treatment received and methodology of measurement). Importantly, there is increasing evidence that poor body composition and specifically, low muscle mass can increase severity of treatment toxicities (Shachar et al., 2016, 2017a; Shachar et al., 2017b). 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 (Brown et al., 2015). 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 (Levy et al., 2008; Given et al., 2001; Silver et al., 2007). 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 (Storer et al., 2012; Granger et al., 2014; Gonzalez et al., 2016). 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 (Granger et al., 2014). Soyupek et al. (2008) found that in a sample of 87 early-stage colorectal patients, about half (54%) had a handgrip strength < 85% below the reference range Burden et al. (2010). 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 (Harrington et al., 2011). 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 (Brown et al., 2015, 2016; Deldicque et al., 1985). Galvao et al. (2007) 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 (Fig. 2). The changes have important implications in preserving physical function with age and reducing the risk of falls and fractures amongst individuals with cancer. Clearly, regardless of the aetiology, loss of LBM in cancer comes with severe costs. Thus, the identification of novel strategies to maintain or improve muscle mass and strength is of high priority and clinical importance.

## 5. The theoretical potential of Cr supplementation to treat cancer-related physical impairments

There is strong evidence suggesting Cr supplementation can promote the overexpression of genes and proteins related to muscle hypertrophy (Safdar et al., 2008; Deldicque et al., 1985), as well as satellite cell activation (Olsen et al., 2006). Olsen et al. (2006) reported that in healthy humans, Cr supplementation in combination with PRT amplified the increase in satellite cell number and myonuclei concentration in skeletal muscle fibres, 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) (Willoughby and Rosene, 2001). The growth-promoting effects of Cr may be useful in situations where anabolic activity is suppressed, such as muscle wasting diseases, ageing populations, and cancer patients.

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 fibres. PCr content is 5–15% higher in Type II than Type I fibers (Greenhaff et al., 1994; Soderlund and Hultman, 1991) Additionally, the rate of PCr degradation is faster in Type II than Type I fibers during high-intensity, short duration activities. (Greenhaff et al., 1994) 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 (Casey et al., 1996). 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 (Hultman et al., 1991). Therefore, any mechanism capable of increasing intramuscular Cr stores may help to prevent PCr depletion, and delay fatigue, during intense exercise.

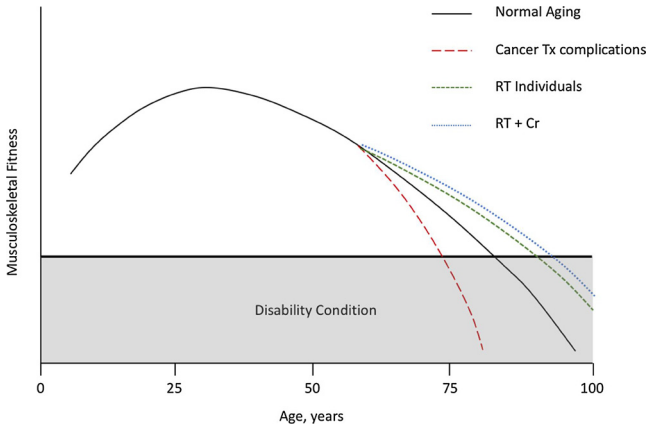


**Fig. 2.** Theoretical model of the role of RT and Cr to attenuate musculoskeletal fitness decline in individuals with cancer. (Modified from Galvão et al. Prostate Cancer Prostatic Dis 2008) Certain cancer therapies can exacerbate declines in muscle mass and strength, leading to an accelerated decline 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 colour).

Earlier work by Harris et al. (1992) 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 (Sipila et al., 1981). 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.

## 6. Cr supplementation in cancer patients

Currently, the studies examining the effects of Cr in cancer patients have failed to show demonstrable benefit in LBM, muscle strength or function with from supplementation. A summary of these studies can be found in Table 2. Jatoi et al. (2017) examined Cr supplementation in 263 colorectal cancer patients (65 ± 11 yrs.) experiencing "anorexia/weight loss syndrome". In this trial, individuals with an incurable malignancy and a life expectancy of ≥12 weeks were randomly assigned to either Cr (20 g/day load × 5 days followed by 2 g/day) or placebo powder with identical dosing. Participants undergoing concurrent chemotherapy or radiotherapy were also eligible. Body weight was assessed weekly for 4-weeks and thereafter monthly while the patient

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

| Authors (year) | Patients | Treatment Modality | Dosage | Protocol duration | Compliance | Exercise program | Results | Adverse Effects related to supplementation |
|---|---|---|---|---|---|---|---|---|
| Jatoi et al. (2017) | 263 cancer patients (65 ± 11 yrs.) with weight loss syndrome | 210 undergoing concurrent chemotherapy | 20 g/day for 5 days then 2 g/day | 39 weeks | nr | n/a | ↔ body weight, appetite, QoL, frailty, grip strength, | None reported |
| Bourgeois et al. (2008) | 9 children (7.6 ± 3.8 yrs.) with ALL undergoing chemotherapy | Maintenance phase of treatment on the Dana-Farber Cancer Institute protocol 2000-2001 | 0.10 g/kg/day | 2 × 16 weeks separated by 6-week wash-out period. | nr | n/a | ↓ BF% Cr, ↑ BF% NH<br>↔ BMD | None reported |
| Norman et al. (2006) | 31 stage III/IV colorectal cancer patients (65.10 ± 12.55 yrs.) undergoing chemotherapy | n = 11: Fluorouracil/folic acid (5-FU FA); n = 9: Fluorouracil/folic acid + Oxaliplatin (5-FU FA + O); n = 11: Fluorouracil/folic acid + Irinotecan (5-FU FA + I) | 20 g/day for 7 days then 5 g/day | 8 weeks | Cr: 84.55 ± 7.77%; PLA: 87.62 ± 5.90% | n/a | ↔ weight, capacitance, KE, HF, BCM, BF; ↑ HG<br>5-FU FA: ↑ phase angle, ECM/BCM ratio | None reported |
| Loenbro et al. (2013) | 30 Head and neck patients treated with radiotherapy | Radiotherapy according to DAHANCA guidelines (www.dahanca.dk) ± chemotherapy (n = 20: cisplatin, 40 mg/m$^2$), n = 4 received Zalutumumab | 5 g/day + 30 g Pro/day | 12 weeks | 69% ingested all supplementation. 19% missed ≤ 3 supplementations, 12% terminated 4 weeks early | 3 day/wk., 3 × 10 total body | ↑ LBM PROCR group, ns↑ PLA ↔ Muscle Strength**, ↔ Physical function** | No major adverse events reported. 2 participants stopped supplementation 4 weeks early due to muscle cramping and mucus production. |

ALL: acute lymphoblastic leukemia; BCM: body cell mass; BF%: body fat percentage; BMD: bone mineral density; Cr: creatine supplementation; ECM: extracellular mass; g: gram; HG: hand grip; HF: hip flexion; kg: kilogram; KE: knee extension; LBM: lean body mass; MF: muscle function; NH: natural history group; PLA: placebo; PROCR: Protein + creatine supplementation; n/a: not applicable; nr: not reported; QoL: quality of life; yrs.: years old ↑: increase; ↓: decrease; ↔: no change; **compared to Placebo.

remained on Cr or placebo. Appetite, QoL, frailty and grip strength were also assessed. The primary endpoint was the percentage of patients who gained ≥10% of their baseline weight by 4-weeks. Out of 263 patients, only 3 gained ≥10% of their baseline weight over 4-weeks: 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.

Norman et al. (2006) investigated the effects of 8 weeks of Cr supplementation on muscle function (hand grip, knee extension and hip flexion) body composition and QoL in 31 stage III/IVcolorectal cancer patients (65.10 ± 12.55 yrs.) undergoing chemotherapy (n = 11: Fluorouracil/folic acid (5-FU FA); n = 9: Fluorouracil/folic acid + Oxaliplatin (5-FU FA + O); n = 11: Fluorouracil/folic acid + Irinotecan (5-FU FA + I). Patients were randomized to receive either Cr monohydrate or a placebo. Patients in the Cr group received 20 g/d for the first 7 days, followed by 5 g/d as a maintenance for the remainder of the study. Phase angle (a marker of body cell mass) and increased significantly in the Cr group. Additionally, the ratio of extracellular mass (ECM) to body cell mass (BCM) was significantly improved, though only in the Cr group receiving 5-FU FA. Capacitance was maintained in the Cr group but declined in the PLA group. There were no significant changes in any other assessments of body composition (i.e. body cell mass, or body fat). Whilst there were no significant changes in body weight across the intervention, subgroup analysis revealed that individuals in the Cr group receiving 5-FU FA improved weight significantly (73.50 ± 4.98–76.92 ± 5.25 kg, p = 0.028). Grip strength of the dominant hand improved in both groups, whereas individuals in the Cr group experienced improvements in grip strength of the non-dominant hand. Knee extension, hip flexion strength and QoL did not improve in either group. Importantly, this study had no exercise component across the 8 weeks. The authors concluded that Cr supplementation may be important in improving indices of body composition in individuals with colorectal cancer undergoing less aggressive chemotherapy, though they urged caution in interpretation due to the small sample size.

Bourgeois and colleagues (Bourgeois et al., 2008) investigated the effects of Cr supplementation with children (7.6 ± 3.8 yrs.) on the maintenance phase of treatment on the Dana-Farber Cancer Institute protocol 2000–2001for acute lymphoblastic leukemia for two periods of 16 weeks separated by a 6-week “wash out” period. Importantly, whilst there are no studies directly comparing the effects of Cr supplementation in children and adults, several studies exist in children/young adults demonstrating improvements in strength, FFM and anaerobic performance following Cr supplementation that are consistent with those seen in adults (Tarnopolsky et al., 2004; Grindstaff et al., 1997). 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. (2013) examined feasibility and efficacy of 12 weeks of PRT in combination with protein and Cr supplementation (PROCR) in head and neck cancer patients. Patients were randomized into two groups: A PROCR group undergoing a seven-day pre-trial creatine loading protocol (20 g/day for 7 days) followed by 12 weeks of PRT with Cr (5 g/day) and protein (30 g/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.

Collectively, the current studies examining the effects of Cr supplementation on muscle mass, body composition, strength and function have failed to demonstrate beneficial effects. As stated in Section 2 above, t the primary mechanism of Cr supplementation lies in its ability

to supply 'extra' energy to target tissues, helping to enhance exercise capacity and maximise training adaptation (Kreider et al., 2017; Buford et al., 2007). Muscle inactivity may contribute to a decrease in Cr uptake, and therefore compromise the effect of Cr supplementation on LBM and strength. Thus, a plausible reason for null findings in the studies investigating Cr supplementation in cancer is the lack of an exercise stimulus, particularly given that Cr uptake by skeletal muscle is modulated by muscle activity (Harris et al., 1992). It is worth noting that some studies have failed to find beneficial effects of Cr supplementation on body composition and muscle function in healthy older adults. A number of factors may contribute to the inconsistences in the literature, including no description of physical activity levels, the presence of chronic disease, medications, or short-term protocols (< 4 weeks) (Rawson and Clarkson, 2000; Rawson et al., 1999). However, Lønbro et al (Loenbro et al., 2013) did combine Cr supplementation with PRT and found no additive effect of Cr on LBM when combined with PRT. The participants in this study had completed radiotherapy and chemotherapy prior to enrolling in the trial. Whilst it is unclear why there were no additive effects of Cr supplementation, cancer treatments may result in a different physiological profiles that may affect the pharmacokinetics (and subsequent ergogenic effect) of Cr. Further, individuals with cancer who are undergoing or have completed treatment may not have the capacity to obtain sufficient additional training volume to allow for an additive effect to be realised. Ultimately, the lack of findings of Cr supplementation combined with PRT on LBM, muscle strength and function in individuals with cancer are interesting, particularly when compared to apparently healthy adults. These results highlight the need for studies in this area (particularly combining Cr supplementation with PRT), specifically designed to examine the effect of Cr supplementation on LBM, muscle strength and physical function in patients with cancer.

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. (2018) 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. (2015) found the highest prevalence of cachexia in pancreatic cancer (98.9%), gastric cancer (76.5%) and oesophageal cancer (52.9%). Geriatric cancer patients are particularly vulnerable, given the already low muscle mass in this population. Indeed, Prado et al. (2008) 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 (Galvao et al., 2008).

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 (Peterson and Mozer, 2017; Prado et al., 2008). 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.

## 7. Dosing protocols

While the optimal supplementation protocol to elicit the greatest changes in LBM and muscle function in cancer patients remains unknown, the protocol most often described in the literature is referred to as a "loading" protocol, followed by a low dose "maintenance" period. This protocol is characterised by ingesting 0.3 g/kg/day of Cr for 5–7 days (approximately 5 g of Cr taken 4 times daily) followed by 5 g/day thereafter to maintain creatine stores. Research has demonstrated a 10–40% increase in muscle Cr and PCr stores using this protocol (Kreider et al., 2017). Alternatively, doses of 3–5 g day without an initial "loading protocol" result in a more gradual increase in muscle creatine, typically at least 28 days that results in similar levels of saturation (Kreider et al., 2017; Hultman et al., 1985). Though creatine stores will also be eventually saturated with this protocol, the effects on exercise performance and subsequent adaptations will likely be blunted until creatine stores are fully saturated. Consequently, it would be advantageous for researchers investigating the effects of Cr supplementation in combination with resistance training, to incorporate the loading phase of 0.3 g/kg/day of Cr for 5–7 days prior to the onset of training to enhance the likelihood of experiencing improvements in exercise performance and adaptations.

## 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 (Kreider et al., 2017; Buford et al., 2007), 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 (Kreider et al., 2017; Buford et al., 2007; Bender et al., 2008). 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 (Lugaresi et al., 2013; Neves et al., 2011; Poortmans et al., 1997; Gualano et al., 2008). In fact, Cr supplementation is being considered as a means to improve musculoskeletal and neurological functioning in patients with chronic kidney disease (Wallimann et al., 2017). 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 to 5 years, and doses up to 10 g/day, with no adverse effects of supplementation or impact on renal dysfunction reported (Bender and Klopstock, 2016; Bender et al., 2006; Writing Group for the, N.E.T.i.P.D.I. et al., 2015)

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 (Kreider et al., 2017; Buford et al., 2007). Researchers have conducted a meta-analysis and reported no evidence of altered hydration status or thermoregulation following Cr supplementation (Lopez et al., 2009). Lønbro et al. (Loenbro et al., 2013) had two participants cease supplementation due to muscle cramping and mucus production with a beverage containing creatine (5 g), maltodextrin (5 g) protein (23 g), carbohydrate (2 g) and fat (2 g). This is somewhat surprising given the overwhelming body of evidence reporting no detrimental effects of short- or long-term Cr supplementation on kidney function, gastrointestinal distress, muscle dysfunction or hydration status (Kreider et al., 2017; Buford et al., 2007; Bender et al., 2008; Lugaresi et al., 2013; Neves et al., 2011; Poortmans et al., 1997; Gualano et al., 2008). Additionally, it is unclear whether the muscle cramping/mucus production was due to the Cr supplementation, the mix of ingredients in the supplement, or other external factors. Nevertheless, these findings offer insight into the potential for Cr supplementation to be associated with mild discomfort in some individuals with cancer. 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.

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 (Jatoi et al., 2017). Nevertheless, application in various cancer contexts is still largely theoretical, with research in this area remaining sparse. Currently, no studies investigating the effects of Cr supplementation in cancer have shown any effect on LBM, muscle strength or function. 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.

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