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REGENERATIVE BIOLOGY AND MEDICINE IN OSTEOPOROSIS (S BRYANT AND M KREBS, SECTION EDITORS)

Exercise and Nutritional Approaches to Combat Cancer-Related Bone and Muscle Loss

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Abstract

Purpose of Review The aim of this narrative review is to summarise recent literature on the effects of exercise and nutrition interventions alone or in combination on muscle and bone loss in people with cancer.

Recent Findings There is emerging evidence to support the inclusion of targeted exercise and nutrition strategies to counter loss of muscle and bone associated with cancer treatments. Although research in this field is advancing, the optimal exercise and nutrition prescription to combat cancer-related bone and muscle loss remain unknown.

Summary This review identifies specific components of nutrition and exercise interventions that are promising although require further exploration through studies designed to determine the effect on muscle and bone. A focused research effort is required to elucidate the full potential of exercise and nutrition intervention for people with cancer at risk of bone and muscle loss.

Keywords Cancer · Sarcopenia · Bone · Muscle · Nutrition · Exercise · Diet

Introduction

People with cancer experience muscle and bone loss at rates of up to 10-fold the usual age-related losses observed in non-cancer populations [1, 2]. This has significant health and lifestyle implications for people undergoing or recovering from cancer treatment because of the associated (up to 50–60%) increased risk of osteoporosis, falls and/or fractures [3, 4] and four-fold increased risk of mortality [5].

The prevalence of sarcopenia, defined as low muscle strength, muscle mass and/or physical performance, is reported to range from 3 to 12% in studies of people with colorectal or prostate cancer [6, 7]. Most studies in cancer have assessed muscle mass alone using a range of different techniques, with the prevalence of low muscle mass estimated to range from 25 to 60% of patients across multiple cancer diagnoses [5, 8, 9]. Metabolic changes, including increased systemic inflammation and oxidative stress, tumour-related factors and/or cancer therapies, combined with reduced nutritional intake and physical inactivity, are the primary drivers of loss of muscle mass, strength and function, in people with cancer (Fig. 1) [10, 11]. Furthermore, studies in ageing populations have found accelerated losses in muscle mass appear to increase inflammation, oxidative stress and insulin resistance and reduce resting energy expenditure, all of which can have detrimental effects for cardiometabolic health [12]. Recent studies have also demonstrated that people with or recovering from cancer who have sarcopenia have decreased survival time, time to tumour progression and are at more than double the risk of developing dose limiting treatment toxicities [9, 13, 14]. At present, there are no routinely prescribed pharmacological approaches to counter cancer-related muscle loss, highlighting the important role of modifiable lifestyle factors such as exercise and nutrition.

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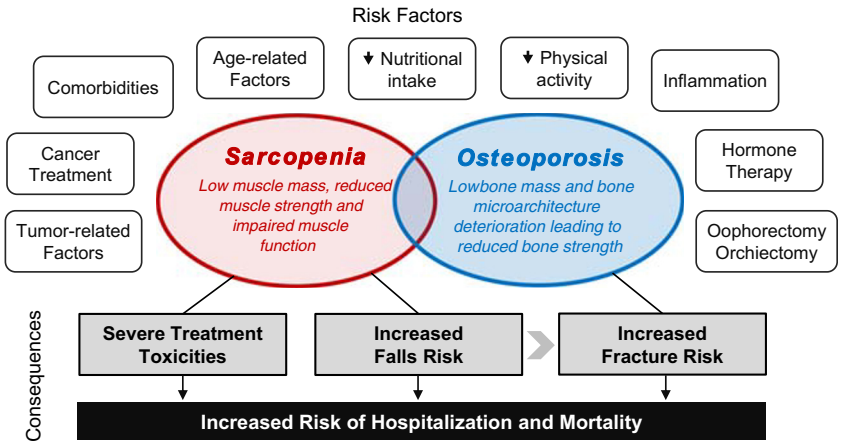

Fig. 1 Factors contributing to loss of muscle mass and bone in cancer and consequences to health

Cancer-related bone loss is largely a consequence of impaired balance between bone formation and resorption from treatment-induced hypogonadism, particularly occurring with oestrogen receptor modulators and aromatase inhibitors (AI) in breast cancer and androgen deprivation therapy (ADT) in prostate cancer [2]. Prospective studies of men with prostate cancer receiving ADT have reported accelerated losses in areal bone mineral density (BMD) in the first year of up to 6.5% at the hip and 8% at the spine compared to the typical 0.5–1.0% annual age-related loss observed in healthy older men [15]. Similarly, women with breast cancer can experience up to 5–9% bone loss at the lumbar spine as soon as 1 year following various treatments (AI and gonadotropin releasing hormone [GnRH] analogues), which is comparable to the amount of bone lost during the 5–10-year post-menopausal period [2, 16]. Loss of bone mass can also occur as a result of chemotherapy or radiotherapy treatment, which is of particular concern considering their widespread use across most cancer diagnoses [2, 17••, 18]. The impact of accelerated bone loss related to cancer treatment is significant as it has been associated with a 50–60% increased risk for fracture, which has been associated with poorer quality of life and increased mortality [2, 19, 20]. While pharmacological agents are recommended and can prevent bone loss related to cancer treatment [3, 16], there is a need to consider other lifestyle factors such as calcium, vitamin D and exercise that target factors both including BMD as well as other factors that can reduce the risk of fractures.

In this brief narrative review, we will summarise recent literature relating to the role of exercise and nutrition, alone and in combination, for optimising muscle and/or bone loss in people with cancer, with a focus on randomised controlled trials and systematic reviews and/or meta-analyses. We also aim to highlight gaps and future directions in the fields of cancer-related exercise and nutrition research to counter muscle and bone loss to reduce falls and fracture risk.

Effect of Exercise Intervention on Cancer-Related Bone and Muscle Loss

Current clinical and consensus guidelines for the management of bone health in people with cancer recommend exercise, particularly progressive resistance training (PRT), weight-bearing impact activities or multi-modal programs, as an important approach to manage cancer-related bone loss [3, 15, 16]. However, the level of evidence to support these recommendations is limited. The 2019 American College of Sports Medicine (ACSM) exercise guidelines for cancer survivors indicate that there was moderate evidence for a positive effect of exercise on bone health in people with cancer, with the majority of included studies conducted in breast and prostate cancer [21].

Two recent systematic reviews and meta-analyses in breast cancer (7 randomised controlled trials (RCTs) enrolling 1199 women) and adult cancer survivors (6 RCTs enrolling 814 participants) both reported negligible effects of prescribed exercise for ≥ 6–12 months on the spine or proximal femur BMD [17••, 22]. Importantly, subgroup analyses in one of the reviews revealed a positive effect on lumbar spine BMD in three studies with regimes that included PRT combined with impact exercise [17••]. A recent trial also reported a positive, albeit modest, effect of a targeted PRT and impact loading program on bone health in men with prostate cancer treated with ADT. In this three-arm, 12-month RCT in 154 ADT-treated men with prostate cancer, moderate-high-intensity PRT (2–4 sets, 6–12 repetitions, 6 exercises) plus impact exercise (2–4 sets, 10 repetitions, 3–4 exercises; e.g. skipping, hopping, leaping, drop-jumps) completed four times per week (two supervised, two home-based) was found to attenuate lumbar spine BMD loss (− 0.6% vs − 1.8%), but not hip BMD, compared to controls after 12-months; there was no effect on BMD at any site in the study arm completing PRT plus aerobic exercise [23]. However, three other 12-month trials have reported mixed findings following a thrice weekly moderate-intensity PRT plus impact exercise (two-footed

jumping) program relative to sham exercise (flexibility training) on BMD in men with prostate cancer treated with ADT [24], prematurely menopausal breast cancer survivors > 1-year post-treatment [25] and post-menopausal breast cancer survivors [26]. Two of these studies reported no effects of the exercise program on hip or lumbar spine BMD [24, 25], while the study in postmenopausal breast cancer survivors reported that lumbar spine BMD was preserved (+ 0.4% vs − 2.3%) but there was no effect on hip BMD [26]. In healthy older adults, similar multi-modal exercise programs have been shown to improve hip and/or spine BMD by ~ 1–2% after 12–18 months [27, 28]. This suggests that exercise alone may only preserve or attenuate bone loss at the lumbar spine in men with prostate cancer treated with ADT or women with breast cancer, although this represents a positive finding given the marked bone loss typically observed. We were unable to identify any other trials which evaluated the effects of exercise and bone health after cancer diagnoses other than breast or prostate cancer.

Hip fractures are the most devastating of all fractures because they are associated with considerable morbidity and mortality [29]. Given that none of the exercise interventions across the various cancer populations has been able to protect against hip bone loss, there is a need to understand why all programs have been ineffective. A possible explanation is that some of the studies were of insufficient duration, did not include appropriate exercises designed to specifically load the muscles attached to or near the hip and/or that the loads were not of sufficient magnitude, rate or distribution (novel/diverse loading pattern) to stimulate an osteogenic response. Indeed, several RCTs that reported no effect on hip BMD did not include weight-bearing impact exercises [30–32], prescribed only low-intensity resistance exercise [30, 31] and/or were 6 months or shorter in duration which is not sufficient to detect true physiological skeletal changes since the typical bone remodelling cycle to mineralisation can take up to 6–8 months [30, 31, 33]. In partial support of the importance of diverse loading patterns for bone adaptation, a 32-week RCT in 57 ADT-treated men with prostate cancer reported that 2–3 weekly football training sessions which included resistance training and a range of novel, intermittent impact loading activities preserved total hip and femoral BMD relative to controls (+ 0.4 to 1.0% vs − 0.7 to − 1.1%) [34]. Despite these positive findings, there is insufficient evidence to inform the optimal type and dose of exercise to improve bone health in cancer populations.

With regard to the effects of exercise on muscle-related outcomes in people with cancer, there is compelling evidence to support beneficial effects on muscle strength and physical function [35, 36, 37••, 38]. For instance, recent meta-analyses and an umbrella review of exercise in people with cancer reported significant overall positive effects of resistance and/or aerobic exercise interventions on muscle strength [36, 38], self-reported [35, 38] and objectively measured physical function such as chair-rise test performance [37••]. In addition, the greatest effects were observed with supervised rather than unsupervised exercise training [35, 37••, 38], and muscle strength interventions that were progressive in nature led to the greatest gains [37••]. Similar to the studies in bone, most of the available exercise trials have been conducted in breast cancer survivors, and to a lesser extent, prostate cancer survivors, although recent studies in people with haematological, gastrointestinal, gynaecological and lung cancer have reported positive effects of exercise (resistance and/or aerobic training) on muscle strength and function [35, 37••, 38].

Whether exercise training has a positive effect on muscle mass in people with cancer is less clear. Recent meta-analyses in prostate cancer have reported mixed findings from interventions prescribing PRT alone or combined with aerobic or impact exercise, with one reporting no significant effect (0.5 kg, $P = 0.44$) [39] and the other reporting a positive effect (1.0 kg, $P = 0.03$) [40] on total body lean mass. However, both these meta-analyses reported beneficial effects of exercise on upper (3.2 to 5.2 kg) and lower body (27.5 to 28.2 kg) muscle strength [39, 40]. These findings are consistent with recent 12-month studies in ADT-treated men that reported negligible effects of resistance-based training on lean mass, despite gains in upper and lower body muscle strength [23, 41]. The lack of an effect on lean mass in these studies may be due to the moderate-intensity resistance training prescribed (60–80% maximal strength) not being sufficient, particularly considering the suppression of testosterone with ADT may blunt the hypertrophic response to resistance exercise. Despite these mixed findings, a recent RCT in 100 overweight or obese sedentary breast cancer survivors reported positive effects of a 4-month, thrice weekly combined resistance (3 sets, 10–15 repetitions, 8 exercises, 60–80% maximal strength) and aerobic (up to 150 min, 65–80% heart rate maximum) training program relative to usual care on total body lean mass (7.7 kg net difference between groups) and muscle strength (10–30 kg net differences) [42]. This was likely due to women receiving one-on-one supervision and high adherence to the training program (96%) and the women having low baseline fitness and physical activity levels [33, 42]. However, two other recent RCTs which quantified changes in lean mass following 9–12 months of resistance plus aerobic training in breast cancer survivors taking AI reported mixed findings [32, 43]. One study in 121 women reported a 1.2 kg significant net benefit ($P = 0.03$) compared to controls [32], while a smaller study in 36 women reported a non-significant 0.7 kg net difference ($P = 0.32$) [43]. The magnitude of change in lean mass within the exercise groups alone was similar in both studies, so differing rates of muscle loss within the control groups appear to have led to the contrasting between group effects. These contrasting findings may also be due to varying sample size and intervention duration, given that resistance training

prescription and participant characteristics were largely similar in each study.

In summary, there is emerging evidence to support the benefits of multi-modal exercise training incorporating PRT combined with weight-bearing impact activities as an approach to attenuate lumbar spine bone loss and preserve muscle mass, strength and function in people with cancer, but questions still remain as to the optimal type and dose (frequency, intensity, duration) of training and whether similar benefits are observed across different cancer populations.

Effect of Nutrition Intervention on Cancer-Related Bone and Muscle Loss

Current clinical guidelines for optimising bone health recommend a calcium intake of 1200 to 1500 mg/day through diet, supplements or both and vitamin D supplementation as necessary to achieve a serum 25-hydroxyvitamin D level of > 75 nmol/L for prostate cancer [15], and routine use, albeit unspecified dose, of calcium and vitamin D supplements for breast cancer [3]. Medical guidelines for management of prostate cancer also recommend calcium and vitamin D supplementation, without specifying doses, for men prescribed bisphosphonates [44]. Despite these recommendations, there is little or no evidence to support the efficacy of calcium and/or vitamin D as an approach to counteract cancer-related bone loss and reduce fracture risk [19, 45]. A previous review of 12 clinical calcium and/or vitamin D studies in men with prostate cancer undergoing ADT treatment reported that 500–1000 mg/day of calcium and 200–500 IU of vitamin D/day was not effective to prevent loss of lumbar spine or hip BMD [45]. Similarly, data from 16 studies revealed that 500–1500 mg of calcium and 200–1000 IU of vitamin D was found to be inadequate to prevent bone loss in women undergoing breast cancer therapy [46]. In both these reviews, concerns were raised about the potential safety of calcium and vitamin D supplementation with regard to cardiovascular disease risk, but there is no evidence in cancer patients to support any adverse effects [45, 46]. A previous systematic review and meta-analysis of 32 prospective studies did report that increased dairy or calcium intake was associated with an increased risk of prostate cancer, but no association was observed with supplemental or non-dairy calcium, suggesting that other components of dairy rather than fat and calcium may increase prostate cancer risk [47]. Similarly, calcium supplementation at doses < 1500 mg/day has been shown to either have no influence on prostate cancer progression [48] or to reduce prostate cancer risk [49] and slow the rate of PSA increase [50]. Moreover, in men diagnosed with prostate cancer, total milk/dairy intake after diagnosis has not been found to be associated with a greater risk of lethal prostate cancer, with evidence of a decreased risk in those with a high intake of low-fat dairy [51]. Similar results have been reported for vitamin D with a systematic review and meta-analysis reporting no evidence of dietary intake and serum levels of vitamin D increasing the risk of developing prostate cancer or of disease progression [52]. The limited available evidence to date suggests that calcium and/or vitamin D supplementation is safe in ADT treated men, but may not be effective in ameliorating the accelerated bone loss with ADT. No studies were located on nutrition and bone health for cancer diagnoses other than prostate cancer.

In terms of preventing cancer-related muscle loss and malnutrition, current guidelines on nutrition recommend early intervention, prior to severe muscle depletion, using increased energy (20–30 kcal/kg/day) and protein (1–1.5 g/kg/day) intake as a primary strategy across all cancer diagnoses [53, 54]. Recommended approaches to achieve this include individualised dietary counselling, escalating to oral nutrition supplements (ONS), enteral or parenteral nutrition, as clinically indicated, with clinical guidelines stating strong evidence this improves nutritional intake, body weight, self-reported physical function and quality of life [53–56]. An important unanswered question for cancer patients is whether there is an optimal nutrition prescription in regard to the type, dose and timing of protein and other nutritional components to support maintenance of muscle mass. Current nutrition guidelines state further research is required to determine the effect of increased protein intake of up to 2.0 g/kg/day, composition of protein and the effect of particular amino acids or metabolites on muscle mass to support clinical recommendations in cancer [53]. Recent studies in this area include a 12-week blinded RCT comparing a whey protein isolate (WPI) supplement (13.5 g protein) to a placebo group, during chemotherapy for colorectal cancer, where preliminary analysis of 47 participants found significantly improved muscle mass in the intervention group (+ 2.7%) after chemotherapy compared to placebo (− 2.4%) [57]. Cereda et al. [58] undertook a RCT comparing nutrition counselling with or without a WPI supplement (20 g protein) in 166 people with advanced cancer undergoing chemotherapy. The WPI supplement group had significantly greater improvements in muscle mass (net difference, + 0.46 kg/m^2) and handgrip strength (+ 2.3 kg) after 12 weeks. A 2019 systematic review and meta-analysis of 15 RCTs investigated the effect of β-hydroxy-β-methylbutyrate (HMB) on muscle mass, finding a small positive effect on muscle mass (SMD = 0.25) and strength (SMD = 0.31) from HMB in a variety of clinical conditions, including two studies in cancer, although there were high levels of bias in the included studies [59]. Collectively, these studies indicate some benefit of specific types of protein or amino acid metabolites on muscle mass in people with cancer. While the optimal dose of protein is still to be determined, the Protein Recommendation to Increase Muscle (PRIME) RCT is currently underway testing the efficacy of a range of protein intakes from 1.0 up to 2.0 g/kg/day on muscle mass in colorectal cancer (Clinicaltrials.gov NCT02788955).

Omega-3 fatty acid supplements rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are thought to mitigate muscle wasting through various inflammatory pathways [60]. Historically, there have been mixed findings from intervention studies of omega-3 supplementation on lean mass in multiple cancer and treatment types [61, 62], which is likely due to variation in omega-3 or EPA/DHA dose, adherence and supplement duration. Several recent studies have reported a positive effect of omega-3 fatty acids on muscle mass, along with a meta-analysis of 12 RCT's of dietary counselling, high-energy oral nutrition supplements (ONS) or ONS enriched with protein and n-3 polyunsaturated fatty acids during chemo-radiotherapy treatment for multiple cancer diagnoses [63••]. The meta-analysis reported an overall significant benefit on total body weight (+ 1.31 kg) and attenuation of muscle loss only in studies using high protein and n-3 polyunsaturated fatty acid-enriched ONS [63••]. However, the authors note compliance with the nutrition interventions was poor or inadequately reported and interventions were often of insufficient length to expect a benefit on outcomes. A recent RCT comparing nutrition intervention with ONS enriched with omega-3 fatty acids and HMB, with multivitamin supplementation, peri-operatively (4-weeks pre- and 4-weeks post-radical cystectomy) in 61 people with bladder cancer, reported 1.5 kg less weight loss and 1.8 cm^2/m^2 less reduction in skeletal muscle index in the ONS group compared to the multivitamin group at 4 weeks after surgery [64]. The authors reported that total protein intake reduced significantly in both groups at 4 weeks post-operatively while there was no difference in energy intake between groups. The protein and energy composition of the ONS was not reported making interpretation of the results difficult. While the benefits reported in these recent studies may be due to the combination of omega-3 with protein-enriched ONS, further research is required to confirm this.

In summary, while likely to be safe, there is limited evidence for the efficacy of calcium and/ or vitamin D supplementation to prevent loss of BMD in people with cancer. There is some evidence for a benefit of protein supplementation, alone or in combination with omega-3 fatty acids, in attenuating cancer-related muscle loss, although unanswered questions remain regarding optimal protein dose, type and timing. A recent review by Prado et al. [65••] of nutrition interventions to treat low muscle mass reported similar findings for protein and omega-3. The authors also looked at glutamine, creatine and carnitine supplementation concluding there were insufficient studies in cancer to recommend use of these supplements in clinical practice.

Combined Effect of Exercise and Nutrition on Cancer-Related Bone Loss

Given that exercise and nutrition, particularly calcium and vitamin D, are independently reported to have some positive effects on bone health across various cancer diagnoses, combining these approaches may produce additive or synergistic skeletal benefits. There is a sound rationale to support an interactive effect of exercise and nutrition on bone health. Exercise is required to stimulate an adaptive response via bone remodelling, while calcium, vitamin D and other nutrients are important substrates for bone mineralisation [66]. To test whether there are additive or synergistic benefits require a factorial 2 × 2 design RCT with four groups (exercise and no-exercise combined with nutrition or placebo (no nutrition)) and an adequate sample size. Several previous meta-analyses examining the interaction between exercise and calcium in pre- and post-menopausal women without cancer have reported greater effects of exercise on BMD at dietary calcium intakes ≥ 1000 mg/day [67, 68]. In contrast, a number of more recent factorial design trials failed to detect any additive or synergistic effect between exercise with various nutritional factors (calcium-vitamin D fortified milk or vitamin D supplementation) on BMD and other determinants of bone strength (e.g. bone structural properties) in older adults or the elderly [28, 69–71]. The lack of any interaction in these trials are likely due to a number of factors, including the small sample sizes, adequate basal dietary calcium intakes and/or sufficient serum 25OHD concentrations, poor exercise compliance and/or the low volume and intensity of training, and the low vitamin D dose and subsequent moderate increase in serum 25OHD concentrations. To our knowledge, there are no factorial-designed RCTs that have tested whether various nutritional factors can enhance the effects of exercise on bone health in people with cancer. Several recent trials in female cancer survivors assessed the effects of exercise plus calcium-vitamin D supplementation versus calcium-vitamin D supplementation alone on bone health [30, 72], but this does not address the question of whether nutritional factors can enhance the effects of exercise on bone. However, a 24-month trial in 223 postmenopausal breast cancer survivors did evaluate whether a twice weekly low-intensity home-based (9 months) followed by a moderate intensity gym-based (15 months) resistance exercise program could augment the effects of anti-osteoporosis medication (weekly risedronate (35 mg)) plus 1200 mg/day calcium and 400 IU/day vitamin D on hip and spine BMD [73]. After 24 months, medication alone (risedronate, calcium and vitamin D) improved total hip (+ 1.81%) and lumbar spine (+ 2.85%) BMD but the addition of exercise did not result in any significant added benefits (additional increase in total hip + 0.34% and lumbar spine + 0.23%). While exercise adherence in this study was very good (69%) and there were significant exercise-induced increases in muscle strength (10–49%). Based on the findings from exercise trials in healthy postmenopausal women, it is likely that the lack of any added benefits was due to the lack of inclusion of any targeted weight-bearing impact exercises and/or the relatively low-moderate resistance training intensity

prescribed. Further studies are warranted to determine whether nutritional factors, or other osteoporosis medications, can provide additional skeletal benefits to exercise in people with cancer across various cancer diagnoses.

Combined Effect of Exercise and Nutrition on Cancer-Related Muscle Loss

Similarly to their effect on bone, exercise and nutrition also independently have positive effects on muscle health. Combining nutrition and exercise through ingestion of protein following resistance exercise may improve the muscle protein synthesis that occurs following resistance exercise [74]. However, it is only recently that the effect of combined nutrition and exercise interventions on muscle mass or strength in people with cancer has emerged in the literature. Current guidelines on nutrition for people with cancer recommend exercise in combination with nutrition, based on the evidence that both are anabolic stimuli for promoting muscle protein synthesis [53]. However, the studies referred to as the basis for this recommendation examined the effect of exercise interventions not the combined effect of nutrition with exercise, reflecting the state of the literature at the time these guidelines were developed. Indeed, in the past 5 years, only four RCTs have investigated the effect of combined nutrition and exercise intervention on muscle mass or strength in people with cancer [75–78], while the majority of studies have focused on outcomes such as diet quality and physical activity behaviours in cancer survivors as reflected in recent reviews [79, 80].

In breast cancer survivors ($N = 33$), a 12-week supervised twice weekly resistance training intervention compared to resistance training plus twice daily whey and casein-based protein supplementation (20 g) within 30 min of exercise resulted in significant within group, but not between group, improvements in upper (+ 29–31 kg) and lower body (+ 15–23 kg) strength and lean mass (+ 0.7–1.1 kg) supporting the benefits of resistance training [76]. The lack of any additional benefit of protein in this study may be due to the modest group difference in protein intake between the groups (exercise only group consuming on average 1.0 g/kg body weight compared to 1.2 g/kg body weight in the exercise plus protein supplementation group). A randomised trial of 50 men with prostate cancer observed a small (0.6 kg) improvement in muscle mass following a 12-week resistance and aerobic exercise program (3/week) alongside fortnightly group education on healthy eating, in comparison to participants who received usual care [75]. However, the authors noted that no meaningful change in diet was observed, suggesting the improvement resulted from the exercise component of the intervention. In metastatic or locally advanced lung or gastrointestinal cancer, a 12-week exercise intervention in small groups for 60 min twice weekly in addition to individualised dietary counselling (minimum 3 sessions) to achieve 1.2 g protein/kg body weight resulted in a non-significant improvement in upper and lower body strength, the magnitude of the changes was not reported [78]. No difference in muscle mass was observed in a small group ($N = 22$) of esophagogastric cancer survivors following surgery with or without neoadjuvant treatment who received a 12-week progressive aerobic and resistance exercise program alongside individualised dietary counselling (frequency varied by participant) compared to a group receiving usual care [77]. A limitation of current research on the effect of exercise and nutrition in combination on muscle loss is a lack of factorial 2×2 design RCT to determine additive or synergistic benefits from nutrition with exercise. Furthermore, the majority of the above studies attempted to intervene with nutrition and exercise following the completion of cancer treatment, which may be too late to be effective. There is a vast body of literature demonstrating substantial muscle loss during cancer treatment and while further muscle loss may occur beyond treatment completion [5, 8, 81], a preventative focus may be more successful than treating loss of muscle mass and strength after they have occurred. While current exercise and nutrition studies in people with cancer consistently use a 12-week intervention period, other aspects of the intervention such as frequency and type of exercise (aerobic or resistance training), supervised or unsupervised exercise training, nutrient focus of the dietary intervention and individualised or group delivery of dietary information are highly variable. Some but not all of the current studies suggest evidence for the efficacy of combined nutrition and exercise interventions in attenuating loss of muscle mass or strength [75, 76]. Research in this area is limited by small sample sizes ($N = 22$ to 58) and studies have not been powered to detect changes in muscle mass or strength as the primary outcome. Furthermore, while adherence to the exercise program is generally well-reported, adherence to the nutrition component of the intervention is frequently not reported meaning it is difficult to assess if dietary change has actually occurred.

Multimodal Approaches to Cancer-Related Bone and Muscle Loss

There are currently no studies investigating multi-modal approaches targeting multiple contributory factors to combat cancer-related bone loss. While studies of multi-modal approaches to cancer-related muscle loss are an emerging area, there are few published studies to date. Solheim et al. [82] conducted a phase II trial ($N = 46$) of a multimodal intervention encompassing daily anti-inflammatory drugs, dietary counselling, omega-3 containing oral nutrition supplements and an exercise program (aerobic 2/week, resistance training 3/week) in people with incurable lung or pancreatic cancer undergoing chemotherapy. The trial demonstrated the

feasibility of the intervention, but had no significant effect on muscle mass. The authors are currently completing a phase III study, Multimodal Exercise, Nutrition and Anti-inflammatory medication for Cachexia (MENAC) [83]. Another promising agent to combat cancer-related muscle loss is anamorelin, a ghrelin receptor agonist that acts to stimulate appetite and anabolism [84, 85]. ROMANA I and ROMANA II, two phase III randomised double-blind trials in people with inoperable lung cancer and cachexia, demonstrated a significant increase in muscle mass (net gain 0.99–0.65 kg), but not strength, in those receiving anamorelin over a 12-week period, albeit with no nutrition or exercise intervention [86]. A number of additional ongoing trials are investigating anamorelin. There is substantial scope for further investigation into multimodal interventions to attenuate cancer-related muscle and bone loss, in particular with a preventative focus in high-risk cancer and treatment types.

Conclusion and Future Directions

Evidence for the role of nutrition and exercise, alone or in combination, to counter cancer-related bone loss is emerging but remains limited. Exercise alone may preserve bone loss in breast and prostate cancer, particularly at the spine. There is little to no evidence suggesting calcium or vitamin D supplementation is effective at attenuating bone loss. Studies investigating whether nutrition interventions, with or without osteoporosis medications, have a synergistic effect on exercise interventions to attenuate or improve cancer-related bone loss are required.

Growing evidence suggests a role for nutrition and exercise, alone or in combination to attenuate cancer-related muscle loss. While it appears clear, there is a beneficial effect of exercise on muscle strength and physical function in people with cancer, the effect on muscle mass is less certain and the optimal exercise dose in terms of frequency, intensity and duration to support muscle mass remain unknown. Nutrition intervention, particularly with protein-enriched ONS, seems to have a positive effect on muscle mass, although similar to exercise, the ideal nutrition prescription in regard to type, dose and timing of protein and/or other nutritional components requires further exploration. Studies using combined nutrition and exercise to attenuate muscle loss in cancer are an emerging area and while promising, existing research has methodological limitations that need to be addressed in future trials, including sample sizes with statistical power to detect change in muscle mass and adequate reporting of adherence to interventions. Studies are also required in a more diverse range of cancer types given the current evidence largely draws from trials in people with breast and prostate cancer. Finally, it is clear that unimodal interventions are likely to be less effective than interventions utilising multimodal approaches consisting of nutrition, exercise and pharmacotherapy. While studies are underway investigating multimodal approaches in people with advanced cancer there is a role for similar approaches in early stages of cancer therapy as preventative measures. In view of the potential of exercise and diet interventions to improve the health and quality of life of for people with cancer, research in this area requires greater focus and support. In the meantime, dietitians and exercise physiologists should be included in cancer treatment teams to limit muscle and bone loss where possible.

Compliance with Ethical Standards

Conflict of Interest Nicole Kiss, Brenton J. Baguley, Jack Dalla Via, Steve F. Fraser and Kate A. Bolam declare no conflict of interest. Robin Daly reports grants from Primary Growth Partnership grant via the Ministry of Primary Industries in New Zealand with Fonterra Co-operative Group Ltd. outside the submitted work.

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