The Biological Mechanisms of Cancer-Related Skeletal Muscle Wasting: The Role of Progressive Resistance Exercise
Sadeeka Al-Majid and Haidee Waters
Biol Res Nurs 2008; 10; 7
DOI: 10.1177/1099800408317345

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Cancer cachexia is a state of progressive wasting characterized by loss of adipose tissue and body proteins. Skeletal muscle, the major reservoir of body proteins, contributes substantially to this state of wasting (Bossola, Pacelli, Tortorelli, & Doglietto, 2007; Thomas, 2007). Skeletal muscle wasting is the most prominent feature in cancer cachexia (George et al., 2007). There is no specific clinical definition of cancer-related skeletal muscle wasting; however, cancer cachexia may be defined clinically as involuntary loss of greater than 5% of premorbid weight within a 6-month period (Inui, 2002). Although significant wasting occurs primarily in patients with advanced malignancies, a number of cancer patients show some degree of wasting at the time of diagnosis (Andreyev, Norman, Oates, & Cunningham, 1998; Chute et al., 1985; Wigmore, Plester, Richardson, & Fearon, 1997).

Skeletal muscle wasting is clinically significant because it contributes to decreased responsiveness to cancer treatment and severe dose-limiting toxicities leading to poor prognosis and increased morbidity and mortality (Andreyev et al., 1998; Attaix et al., 2005). Because muscle strength is proportional to muscle mass (Maughan, Watson, & Weir, 1983; Newman et al., 2003), muscle wasting contributes to weakness and reduced functional ability (Argiles, Busquets, Felipe, & Lopez-Soriano, 2005; Muscaritoli,
Bossola, Aversa, Bellantone, & Fanelli, 2006; Stewart, Skipworth, & Fearon, 2006), which in turn diminish the quality of life. Despite its significance, cancer-related skeletal muscle wasting remains a difficult challenge in oncology practice today. A major barrier to effective management of skeletal muscle wasting is the inadequate understanding of its underlying biological mechanisms. A better understanding of these mechanisms may result in the development of more specific interventions to manage the problem.

Several recent reviews by others have focused on the mechanisms of muscle wasting associated with aging and chronic disease conditions including cancer (Lynch, Schertzer, & Ryall, 2007; Melstrom, Melstrom, Ding, & Adrian, 2007; Ventadour & Attaix, 2006). In this article, we discuss several cancer-related skeletal muscle wasting mechanisms and propose that progressive resistance exercise might attenuate muscle wasting by counteracting some of these mechanisms.

Method

We searched Medline, CINAHL, PsychINFO, and Cochrane Central Register of Controlled Trials databases from their inception through November 16, 2007, using the following search terms in various combinations: “cancer” and related terms (e.g., “neoplasm,” “malignancy”); “skeletal muscle wasting” and related terms (“wasting,” “muscle loss,” “cachexia”); “mechanisms”; and “progressive resistance exercise” and related terms (“strength training,” “resistance training”). The search was limited to the English language. We included relevant basic research reports (animal studies), review articles, and randomized and nonrandomized controlled and uncontrolled trials as well as relevant references in retrieved articles. Exercise studies that employed combined endurance and resistance exercise protocols were not included because such protocols preclude forming appropriate conclusions about the specific effects of progressive resistance exercise.

Mechanisms Underlying Cancer-Related Skeletal Muscle Wasting

The mechanisms underlying cancer-related skeletal muscle wasting have received increased attention from researchers over the past two decades. Although some of these mechanisms still remain to be fully elucidated, skeletal muscle wasting clearly occurs because of perturbations in muscle protein metabolism, including decreased muscle protein synthesis, increased muscle protein degradation, or a combination of both (see Figure 1). Such perturbations have been documented in tumor-bearing animals (Emery, Lovell, & Rennie, 1984; Pain, Randall, & Garlick, 1984; Samuels et al., 2001) and in weight-losing cancer patients (Drowzak, Ferrari, Gavazzi, Maiorana, & Bozetti, 1998; Emery, Edwards, Rennie, Souhami, & Halliday, 1984; Lundholm, Bylund, Holm, & Schersten, 1976; Lundholm et al., 1982).

Decreased Skeletal Muscle Protein Synthesis

Evidence suggests that cancer-related depression in skeletal muscle protein synthesis may be related to increased serum level of the tumor-released proteolysis-inducing factor (PIF). This is a 24-kDa sulphated glycoprotein produced by cachexia-inducing tumors (Lorite et al., 2001). It was originally detected in the urine of weight-losing cancer patients but not in the urine of weight-stable cancer patients or weight-losing noncancer patients (Todorov et al., 1996). Patients with pancreatic tumors whose urine was positive for the PIF had significantly greater weight loss (median = 12.5 kg) compared to patients whose urine was negative for this factor (median = 4.5 kg; Wigmore, Barber, Ross, Tisdale, & Fearon, 2000). A PIF of identical characteristics and molecular weight was later detected in the cachexia-inducing murine tumor MAC16 (Todorov et al., 1996). This PIF induced significant loss of lean body mass in mice bearing human melanoma cells (Todorov, Field, & Tisdale, 1999) and induced significant reduction in muscle protein synthesis in vivo (Lorite, Cariuk, & Tisdale, 1997) and in vitro (Eley, Russell, Baxter, Mukerji, & Tisdale, 2007; Smith, Lorite, & Tisdale, 1999). Recent evidence suggests that this PIF decreases muscle protein synthesis by inhibiting protein translation initiation through phosphorylation of the eukaryotic initiation factor 2 (eIF2-α; Eley, Russell, & Tisdale, 2007).

Angiotensin II is another factor that may contribute to cancer-related decrease in muscle protein synthesis (Smith et al., 1999). Angiotensin II induced 40–50% depression in protein synthesis in murine myotubes (Russell, Sanders, & Tisdale, 2006; Smith et al., 1999). Similar to PIF, angiotensin II is thought to decrease muscle protein synthesis by affecting translation initiation (Russell et al., 2006).
Cancer-related depression in skeletal muscle protein synthesis may also be attributed to decreased phosphorylation of the intramuscular amino acid–signaling molecules mammalian target of rapamycin (mTOR) and its downstream target p70 S6 kinase (p70S6k; Eley, Russell, & Tisdale, 2007). Because mTOR and p70S6k play a role in the translation initiation phase of protein synthesis, depression in their activity reduces the rate of muscle protein synthesis (Baar, 2006; Bodine, 2006; Kline, Panaro, Yang, & Bodine, 2007; Mendez, Kollmorgen, White, & Rhoads, 1997; Winningham et al., 1994). Recently, decreased expression and phosphorylation of mTOR and p70S6k was observed in the gastrocnemius muscle of cachectic mice bearing the MAC16 tumor. Feeding these mice with the branched-chain amino acid leucine increased phosphorylation of mTOR and p70S6k, with concomitant increase in gastrocnemius muscle protein synthesis (Eley, Russell, & Tisdale, 2007).

Another factor that may contribute to decreased skeletal muscle protein synthesis in cancer is the decreased level of physical activity, which occurs secondary to weakness and fatigue (Irvine, Vincent, Graydon, & Bubela, 1998; Tisdale, 2006; Yost et al., 2005). Decreased muscle contractile activity depresses the rate of protein synthesis in the skeletal muscle (Paddon-Jones et al., 2005) and leads to muscle atrophy (Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Winningham et al., 1994) possibly by decreasing the activity of the protein-signaling molecules mTOR and p70S6k (Rennie & Wilkes, 2005).

### Increased Skeletal Muscle Protein Degradation

Although decreased protein synthesis plays a role, evidence suggests that cancer-related skeletal muscle wasting occurs primarily because of an increase in the rate of muscle protein degradation (Costelli et al., 2005). The increase in skeletal muscle proteolysis in cancer is attributable to several mechanisms, including activation of proteolytic systems within the skeletal muscle.
Activation of skeletal muscle proteolytic systems. The skeletal muscle contains several proteolytic systems, two of which researchers have suggested may play a role in cancer-related skeletal muscle protein degradation. These include the nonlysosomal calcium (Ca\(^{2+}\)) dependent protease system and the ATP-dependent ubiquitin–proteasome system (UPS). The nonlysosomal Ca\(^{2+}\)-dependent protease system consists of a family of Ca\(^{2+}\)-activated cysteine proteases known as calpains (Bartoli & Richard, 2005). Calpains degrade the structures that keep myofibrillar proteins assembled in the myofibrils, leading to myofibrillar disassembly (Attaix et al., 2005; Baar, Nader, & Bodine, 2006). Calpains do not, however, degrade myofibrillar proteins, nor does their inhibition block muscle protein degradation (Baracos, DeVivo, Hoyle, & Goldberg, 1995). Nevertheless, the ability of calpains to release myofibrillar proteins, which makes them available for degradation, supports calpains’ role as initiators of myofibrillar protein degradation (Bossola et al., 2007; Solomon & Goldberg, 1996; Tisdale, 2005; Williams, Sun, Fischer, & Hasselgren, 1999). Elevated calpains levels were detected in the skeletal muscle of cachectic tumor-bearing rats (Costelli, Tullio, Baccino, & Melloni, 2001).

The major proteolytic system responsible for cancer-related increase in muscle protein degradation is the ATP-dependent UPS (Combaret et al., 2005; Costelli & Baccino, 2000). The main feature of the UPS is tagging defective or damaged proteins with small polyubiquitin chains through a three-step enzymatic process. The tagged/ubiquitinated proteins then enter the S26 proteasome, which breaks them into small peptides (Attaix, Combaret, Tilignac, & Taillandier, 1999; Lecker, Goldberg, & Mitch, 2006).

In nonpathological states, the UPS degrades damaged and defective proteins produced by errors in gene transcription, mRNA translation, or oxidative stressors (Schubert et al., 2000; Tisdale, 2005). However, during cancer, the activity of the UPS increases, leading to accelerated ubiquitination and subsequent degradation of myofibrillar proteins. In tumor-bearing animals, increased expression of the UPS in skeletal muscle is associated with an increased rate of muscle protein degradation (Costelli et al., 2002; Jagoe, Lecker, Gomes, & Goldberg, 2002; Lorite, Thompson, Drake, Carling, & Tisdale, 1998). On the other hand, inhibiting the UPS activity by blocking ATP production prevents protein degradation in incubated skeletal muscle obtained from cachectic tumor-bearing rats (Baracos et al., 1995; Temparis et al., 1994).

Human-participant research provides further evidence for the role of the UPS in cancer-related skeletal muscle wasting. Significant increase in the expression of ubiquitin mRNA and proteosome activity was detected in the rectus abdominis muscle of weight-losing patients with pancreatic and gastrointestinal cancers (Bossola et al., 2001; Bossola et al., 2003; Dejong et al., 2005). Moreover, the expression of the mRNA for ubiquitin–proteasome subunits C2 and C5 increased 3-fold in the rectus abdominis muscle of persons who had colon or pancreatic cancer and an average weight loss of 14.5%, as compared to cancer patients without weight loss and to noncancer patients with weight loss (Khal, Hine, Fearon, Dejong, & Tisdale, 2005).

Increased levels of proinflammatory cytokines. Proinflammatory cytokines—particularly tumor necrosis factor-alpha (TNF-\(\alpha\)), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon gamma (IFN-\(\gamma\))—also play a role in cancer-related skeletal muscle wasting (Argiles, Moore-Carrasco, Busquets, & Lopez-Soriano, 2003; Costelli et al., 1993; Figueras et al., 2005; Zoico & Roubenoff, 2002). Elevated serum levels of these proinflammatory cytokines were associated with a significant loss of skeletal muscle mass in mice bearing the MAC16 and the JHU022 tumors (Cannon et al., 2007). On the other hand, inhibition of TNF-\(\alpha\) prevented skeletal muscle wasting in rats bearing the Yoshida AH-130 hepatoma (Costelli et al., 2002). Similarly, IL-6 receptor antagonists and monoclonal antibodies to IL-6 attenuated cachexia, as determined by total body weight, in mice bearing the C-26 adenocarcinoma (Enomoto et al., 2004; Zaki, Nemeth, & Trikha, 2004).

Human-participant research further supports the role of proinflammatory cytokines in cancer-related muscle wasting. The levels of TNF-\(\alpha\) and IL-6 were elevated in the skeletal muscle of weight-losing patients with ovarian cancer (Dillon et al., 2007), and the circulating level of IL-6 was elevated in cachectic patients with gastroesophageal cancer (Krzystek-Korpacka et al., 2007). Similarly, TNF-\(\alpha\) level was elevated in the serum of pancreatic cancer patients who had a significantly low body mass index (Karayiannakis et al., 2001).

Proinflammatory cytokines TNF-\(\alpha\), IL-1, and IFN-\(\gamma\) increase skeletal muscle ubiquitin gene expression as well as free and conjugated ubiquitin levels (Jackman & Kandarian, 2004). Antibodies...
to TNF-\(\alpha\) reduce skeletal muscle ubiquitin gene expression (Combaret et al., 2002; Garcia-Martinez, Llovera, Agell, Lopez-Soriano, & Argiles, 1994; Llovera et al., 1998) and inhibit the associated increase in muscle proteolysis (Costelli et al., 2002). Thus, proinflammatory cytokines may increase muscle protein degradation indirectly via the activation of the UPS.

**PIF.** Cancer-related skeletal muscle protein degradation has also been attributed to the PIF. This factor induced significant increase in muscle protein degradation in mice (Lorite et al., 1997; Todorov et al., 1996) as well as in murine myotubes (Hussey & Tisdale, 2000; Sanders, Russell, & Tisdale, 2005). A monoclonal antibody to PIF blocked muscle protein degradation in vitro (Smith et al., 1999).

Similar to proinflammatory cytokines, the PIF increases muscle protein degradation via activation of the UPS. Injecting nontumor-bearing mice with the PIF resulted in wasting of the gastrocnemius muscle, which was associated with an increased expression of ubiquitin mRNA levels and various proteasome subunits within the muscle (Lorite et al., 2001). The PIF increases the activity of the UPS by upregulating the activity of the transcription nuclear factor–kappa B (NF-kB; Camps, Iranzo, Bremnes, & Sirera, 2006; Russell, Eley, Wyke, & Tisdale, 2007; Wyke & Tisdale, 2005).

**Angiotensin II.** Angiotensin II has also been implicated in the induction of muscle protein degradation associated with cachexia (Eley, Russell, & Tisdale, 2007). Angiotensin II induces significant increase in protein degradation in murine myotubes (Russell et al., 2006; Smith et al., 1999). Similar to PIF, angiotensin II increases protein degradation by NF-kB-mediated activation of the UPS (Eley, Russell, & Tisdale, 2007; Russell, Eley, & Tisdale, 2007).

### The Role of Decreased Nutritional Intake in Cancer-Related Skeletal Muscle Wasting

Although the depression in food intake that frequently occurs in cancer may contribute to skeletal muscle wasting, evidence suggests that the magnitude of depression in nutrient intake does not correlate with the degree of skeletal muscle wasting seen during cancer (MacDonald, Easson, Mazurak, Dunn, & Baracos, 2003). In fact, in some animal models of cancer cachexia, skeletal muscle wasting occurs in the absence of decreased food intake (Al-Majid & McCarthy, 2001; Tanaka et al., 1990). Moreover, the rate of skeletal muscle protein synthesis in tumor-bearing animals is lower than that in the nontumor-bearing controls, irrespective of nutrient intake (Emery, Lovell, et al., 1984; Pain et al., 1984; Samuels et al., 2001; Tisdale, 2003). Newly diagnosed lung cancer patients have increased protein turnover rates in the face of normal food intake (Melville, McNurlan, Calder, & Garlick, 1990). Additionally, nutritional supplementation with or without appetite stimulants increases body fat but fails to increase lean muscle mass in weight-losing cancer patients (Evans et al., 1985; Loprinzi, Schaid, Dose, Burnham, & Jensen, 1993; Simons et al., 1998).

These data suggest that the barrier to lean muscle accretion during cancer may be related to diminished responsiveness to the anabolic effect of nutrients rather than decreased nutrient intake. In sarcopenia, the poor anabolic response to dietary intake, as evidenced by low muscle protein synthesis following the ingestion of essential amino acids, is associated with decreased intramuscular expression and phosphorylation of the amino acid–signaling molecules mTOR and p70\(^{S6k}\) (Cuthbertson et al., 2005). It is not known whether a similar mechanism is operational in the skeletal muscle of persons with cancer. However, a recent report by Eley, Russell, Baxter, et al. (2007) suggests that this mechanism may be operational in mice bearing the MAC16 tumors. Myotubes prepared from these mice showed decreased phosphorylation of mTOR and p70\(^{S6k}\), which was associated with decreased muscle protein synthesis. Interestingly, increasing the phosphorylation of these molecules by feeding the mice with daily doses of leucine (a branched-chain amino acid) resulted in a significant increase in muscle protein synthesis (Eley, Russell, Baxter, et al., 2007). This finding suggests that phosphorylation of these signaling molecules may be necessary to increase skeletal muscle responsiveness to the anabolic effect of food during tumor growth.

Cancer-related skeletal muscle wasting thus occurs because of increased muscle protein degradation accompanied by decreased muscle protein synthesis. Therefore, interventions that aim at attenuating this wasting should focus on decreasing muscle protein degradation and increasing muscle protein synthesis. Interventions that focused only on blocking muscle protein degradation were somewhat successful in attenuating cancer-related skeletal muscle wasting (Tisdale, 2006). However, decreasing skeletal muscle protein degradation may have limited efficacy in the...
face of decreased protein synthesis. Therefore, more effective management should also include interventions that stimulate muscle protein synthesis (Tisdale, 2006).

**Effect of Progressive Resistance Exercise Training (PRT)**

PRT, or strength training, is a potent stimulus of muscle synthesis. It increases muscle mass, endurance, strength, and insulin sensitivity and improves physical functioning (Evans, Roubenoff, & Shevitz, 1998; Pollock et al., 2000; Zinna & Yarasheski, 2003). Thus, the American College of Sports Medicine recognizes PRT as an integral part of a well-rounded exercise program for adults of all ages (Pollock et al., 1998). For the purpose of the current review, PRT is defined as a type of muscular activity in which the muscle generates a progressively higher force over time. It involves a low number of repetitions performed against a progressively higher resistance (Evans, 2004). Regular PRT increases skeletal muscle mass in healthy persons (Hartman, Moore, & Phillips, 2006) and in persons with catabolic conditions such as HIV infection (Grinspoon et al., 2000; Spence, Galantino, Mossberg, & Zimmerman, 1990) and sarcopenia (Binder et al., 2005; Yarasheski et al., 1999; Yarasheski, Zachwieja, & Bier, 1993).

Despite the documented anabolic effects of PRT on skeletal muscle protein synthesis in healthy persons and in persons with various catabolic conditions, the effects of this type of exercise in persons with cancer have not been explored until recently. To date, most of the exercise studies involving persons with cancer have employed endurance exercise (aerobic exercise). A recent systematic review of clinical trials examining exercise in women with breast cancer reported 11 clinical trials, only 2 of which have employed PRT (Cheema, Gaul, Lane, & Fiatarone Singh, 2007). Although endurance exercise has a wide range of physiological and psychological benefits, it does not increase skeletal muscle mass or muscle strength (Pollock et al., 2000). Therefore, PRT should be considered whenever the goal is to increase muscle mass and/or strength.

Four studies, summarized in Table 1, examined the effects of PRT on skeletal muscle mass and/or strength in persons with cancer. Two of these studies examined the effect of PRT in women who were receiving (Courneya et al., 2007) or had recently completed (Schmitz, Ahmed, Hannan, & Yee, 2005) adjuvant therapy for breast cancer. In both of these studies, posttest analyses revealed no change in lean muscle mass in the control group over time. However, women in the PRT group had significant increase in lean muscle mass (Courneya et al., 2007; Schmitz et al., 2005) and strength (Courneya et al., 2007). Because breast cancer is not typically associated with muscle wasting (Campbell, Lane, Martin, Gelmon, & McKenzie, 2007), results from these studies cannot be generalized to patients having cancer-related skeletal muscle wasting.

The remaining two studies (Galvao et al., 2006; Segal et al., 2003) examined the effect of PRT in men receiving androgen deprivation therapy for prostate cancer. Androgen deprivation therapy decreases muscle mass and strength (Smith, 2004). In one of these studies (Galvao et al., 2006), PRT increased quadriceps muscle thickness and upper and lower body strength compared to baseline data. The authors concluded that PRT prevented loss of muscle mass and strength associated with androgen deprivation therapy. However, it should be noted that this study did not include a control group. In the study by Segal et al. (2003), the upper and lower body strength decreased significantly in the control group and increased significantly in the PRT group, suggesting that PRT prevented androgen-associated decrease in muscle strength. However, there was no effect of PRT on lean muscle mass.

Taken together, findings from these studies suggest that PRT may increase muscle strength in persons with cancer, and this increase in strength is associated with increases in physical performance (Galvao et al., 2006) and quality of life (Segal et al., 2003). Nevertheless, because of the limited number of studies, it is hard to make appropriate conclusions about the effect of PRT in persons with cancer.

PRT increases skeletal muscle mass by increasing the rate of muscle protein synthesis (Rennie, Wackerhage, Spangenburg, & Booth, 2004; Wong & Booth, 1990). This anabolic effect of PRT on muscle protein synthesis may be mediated by its effects on cytokines (Figure 2). Muscle contractions stimulate the production and release of the proinflammatory cytokine IL-6 from the contracting muscles in healthy participants (Louis, Raue, Yang, Jemiolo, & Trappe, 2007; Starkie, Ostrowski, Jauffred, Febbraio, & Pedersen, 2003; Steensberg et al., 2002) and in persons with prostate cancer (Galvao et al., 2007). IL-6 exerts anti-inflammatory effects by inhibiting the production...
of the proinflammatory cytokines TNF-α and IL-1 in vitro (Schindler et al., 1990). Additionally, exercise-induced increase in intramuscular IL-6 inhibits the appearance in the circulation of TNF-α in healthy human participants (Starkie et al., 2003). Likewise, infusion of human recombinant IL-6 in human participants inhibits endotoxin-induced increase in plasma levels of TNF-α (Starkie et al., 2003). The anti-inflammatory effect of IL-6 is also demonstrated by its ability to stimulate the appearance in the circulation of the anti-inflammatory cytokines IL-1ra (interleukin-1 receptor antagonist) and IL-10 (Petersen & Pedersen, 2006; Steensberg, Fischer, Keller, Moller, & Pedersen, 2003). IL-10, in turn, inhibits the production of IL-1α, IL-1β, and TNF-α (Pedersen, 2007; Pretolani, 1999).

Progressive resistance exercise also decreases intramuscular production of TNF-α. In frail elderly with age-related muscle wasting, 3 months of PRT induced significant decrease in the expression of TNF-α mRNA and TNF-α protein content in the vastus lateralis muscle compared to pre-exercise and control values. Protein synthesis rate in the vastus lateralis muscle was inversely related to levels of TNF-α protein within the muscle (Greiwie, Cheng, Rubin, Yarasheski, & Semenkovich, 2001).

Together, these data suggest that PRT exerts anti-inflammatory effects by altering the production and release of anti-inflammatory and proinflammatory cytokines. Although these findings are from noncancer persons, they might have relevance for persons with cancer performing PRT.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Cancer</th>
<th>Study Design</th>
<th>Study Groups (N)</th>
<th>Timing of Exercise (During/Post-adjuvant Therapy)</th>
<th>Exercise Frequency, Duration, and Intensity</th>
<th>Outcome Measures/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitz, Ahmed, Hannan, &amp; Yee (2005)</td>
<td>Breast</td>
<td>RCT</td>
<td>Exercise (n = 38); control (n = 40)</td>
<td>Post</td>
<td>1–2 sets of 8–12 reps of each of 9 full-body exercises (involved weight lifting), 2 times/wk, for 26 wks, intensity not stated</td>
<td>Increases UB strength; increases LB strength; increases LBM; decreases % body fat</td>
</tr>
<tr>
<td>Courneya et al. (2007)*</td>
<td>Breast</td>
<td>RCT</td>
<td>Exercise (n = 75); control (n = 75)</td>
<td>During</td>
<td>PRT: 2 sets of 8–12 reps each of 9 exercises, 3 times/wk for 17 wks, 60–70% of estimated 1 RM</td>
<td>Same QoL; increases muscle strength; increases LBM</td>
</tr>
<tr>
<td>Galvao et al. (2006)</td>
<td>Prostate</td>
<td>Uncontrolled</td>
<td>Exercise (n = 10)</td>
<td>During</td>
<td>12 UB and LB exercises performed in two 10-wk phases. Phase I consisted of simple concentric exercises. Phase II consisted of concentric and eccentric exercises progressing from 2 sets of 12 RM during wks 1–2 to 4 sets of 6 RM during wks 8–10.</td>
<td>Increases muscle strength; increases muscle endurance; increases physical performance (chair rise to standing, 6-m walk, 6-m backward walk, stair climb, 400-m walk); increases quadriceps muscle thickness</td>
</tr>
<tr>
<td>Segal et al. (2003)</td>
<td>Prostate</td>
<td>RCT</td>
<td>Exercise (n = 82); control (n = 73)</td>
<td>During</td>
<td>2 sets of 8–12 reps of each of 9 exercises, 3 times/wk for 12 wks, 60–70% of 1 RM</td>
<td>Increases UB strength; increases LB strength; improves QoL; reduces fatigue</td>
</tr>
</tbody>
</table>

NOTE: RCT = randomized controlled trial; wk = week; reps = repetitions; RM = repetition maximum; UB = upper body; LB = lower body; QoL = quality of life; LBM = lean body mass.

a. The study by Courneya et al. (2007) involved two exercise groups: a PRT group and an endurance exercise group; findings from the PRT group compared to the controls are reported here.
Recent evidence suggests that PRT may increase muscle protein synthesis by increasing the phosphorylation of the protein-signaling molecules mTOR and p70S6k (Baar et al., 2006). In one study, an acute bout of resistance exercise resulted in significant phosphorylation of mTOR in rats’ plantaris and tibialis anterior muscles (Parkington, Siebert, LeBrasseur, & Fielding, 2003). Similarly, an acute bout of low-intensity resistance exercise performed at 20% of one repetition maximum enhanced mTOR signaling in the vastus lateralis muscle of young men, and this increase was associated with a significant increase in the rate of protein synthesis within the muscle (Fujita et al., 2007). An acute bout of resistance exercise also increased the phosphorylation of p70S6k, which correlated with an increase in muscle mass following the completion of 6 weeks of exercise training (Baar & Esser, 1999).

However, the evidence supporting the effect of resistance exercise on the protein-signaling molecules mTOR and p70S6k was generated from studies of healthy animals and human participants. It is not clear whether similar mechanisms occur during cancer. Additionally, except for the study by Baar and Esser (1999), previous research employed a single bout of resistance exercise. Therefore, more research is needed to examine whether the transient increase in protein-signaling molecules and the associated increase in the rate of protein synthesis in response to an acute bout of exercise will sustain over an extended exercise training period and result in increased skeletal muscle mass.

Conclusions and Directions for Future Research

Data from a few existing studies suggest that PRT may increase skeletal muscle mass and strength, improve physical functioning, and enhance the quality of life in persons with cancer. However, given the limited number of studies, definite conclusions cannot be made about the effectiveness of PRT in persons with cancer. Clearly, prospective randomized controlled trials are needed. Future trials should include patients with cancers that are likely to induce muscle wasting, such as lung, gastrointestinal, and head and neck cancers, and should determine the feasibility and safety of PRT in such patients. The effect of PRT on the mechanisms implicated in the induction of cancer-related wasting should be explored in future trials. Outcome measures of future trials should include muscle mass and/or muscle cross-sectional area using dual-energy X-ray absorptiometry and computerized tomography scanning, respectively. The effect of PRT on functional outcomes including muscle force production and functional independence should also be examined.

Furthermore, the dose of PRT required to induce positive changes in muscle protein metabolism in cancer patients needs to be ascertained. Reports from such trials should explicitly define the PRT protocol with respect to intensity, frequency, number of repetitions, duration, specific exercises performed, equipment used, and information on the presence or absence of training supervision. Information regarding participant adherence to the exercise program must also be reported.

Recently, Dillon et al. (2007) reported a significant increase in vastus lateralis muscle protein synthesis in women with ovarian cancer following the ingestion of amino acids. However, it is not known whether this acute anabolic effect in response to amino acids will continue with chronic ingestion of amino acids or whether it will have positive effects on muscle mass. Findings from several studies suggest that nutritional supplementation with branched-chain amino acids (Eley, Russell, & Tisdale, 2007) and eicosapentaenoic acid (EPA; Beck, Smith, & Tisdale, 1991; Fearon et al., 2003; Moses, Slater, Preston, Barber, & Fearon, 2004) may attenuate loss of lean body mass by decreasing muscle protein degradation. Because both PRT and nutritional supplementation show some promising results in terms of their effect on cancer-related skeletal muscle metabolism during cancer,
their combined effect should be explored in future trials. Intervening at the time of diagnosis, before skeletal muscle wasting and deterioration of functions are severe, might produce more positive outcomes.

In closing, cancer-related skeletal muscle wasting occurs because of an imbalance between muscle protein synthesis and muscle protein degradation. Both decreased synthesis and increased degradation have been documented in the tumor-bearing host. Although increased degradation is the primary mechanism, a combination of interventions targeted at both increasing synthesis and decreasing degradation are needed to attenuate this muscle wasting.

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