Scientific Research Publishing

Journal of Cancer Therapy, 2022, 13, 497-506
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Resistance Exercise to Mitigate Cancer Cachexia: Molecular Mechanisms and Practical Applications

Charles Paul Lambert[1,2]

[1]University of California, San Diego, USA
[2]Lambert Relentless R&D, LLC, Alexandria, USA
Email: Clcpl368@gmail.com

How to cite this paper: Lambert, C.P. (2022) Resistance Exercise to Mitigate Cancer Cachexia: Molecular Mechanisms and Practical Applications. *Journal of Cancer Therapy*, **13**, 497-506.
https://doi.org/10.4236/jct.2022.138044

Received: July 1, 2022
Accepted: July 30, 2022
Published: August 2, 2022

Abstract

Background: Fifty-eighty percent of all cancer patients are afflicted by cancer cachexia and 20 percent die due to cancer cachexia. **Purpose:** From this narrative review, I will make a case for utilizing resistance exercise training from a molecular mechanistic standpoint and provide insight in how it can be used in a hospital setting. **Method:** PubMed Search and review of the literature. **Discussion:** The loss of about 9 percent of lean body mass is related to lower survival in metastatic colorectal cancer. Chemotherapy is also related to muscle mass loss. Resistance exercise training increases muscle protein synthesis and net muscle protein balance towards anabolism in healthy volunteers. Resistance exercise has shown to reduce the secretion of proinflammatory cytokines from monocytes and reduce toll-like receptor-4 expression on monocytes. Resistance exercise training has been shown to reduce lean body mass losses and improve function in cancer patients. **Conclusion:** All in all, resistance exercise training has been shown to alter molecular mechanisms that lead to muscle protein gains and is an effective means to improve function and reduce lean body mass losses in cancer with few side effects.

Keywords

Muscle Wasting, Oncology, Exercise, Recovery

1. Introduction

Cancer cachexia affects 50% - 80% of all cancer patients [1] with the greatest effect in pancreatic, gastrointestinal, and certain lung cancers. Death by cachexia happens in at least 20% of all cancer patients. The administration of novel mo-

lecular interventions is therefore imperative to the treatment of cachexia along with more traditional treatments such as radiation, chemotherapy, and surgery. Although a popular method for fitness enthusiasts, resistance exercise training, popularly called "weight training" has not been universally utilized to treat cancer cachexia. In this review, I will make a case for utilizing resistance training in cancer patients from a molecular mechanistic standpoint and provide insight in to how it can be used in the hospital setting.

2. Effect of Cancer on Muscle Protein Balance and Survival

Elevated cytokines in cancer, primarily IL-6 and TNFalpha act to inhibit muscle protein synthesis and stimulate muscle protein breakdown. This effect of cytokines has been reviewed in a recent Open Access book chapter [2].

Blauwhoff-Buskermolen *et al.* [3] reported that in 67 patients with metastatic colorectal cancer, that a 9% loss of muscle was the cut point for survival duration. Those with a loss of 9% or more had statistically significant lower survival rate than patients with less than a 9% loss of muscle. This relationship remained when survival was adjusted for sex, age, baseline lactate dehydrogenase levels, comorbities, metatasteses to one organ or many organs, treatment line, or tumor progression when evaluated initially by CT scan.

3. Chemotherapy, Relation to Muscle Loss and Muscle Mass as a Predictor of Chemotherapy Dose

Klassen *et al.* [4] showed that after chemotherapy, there was a substantial loss of muscle strength in the lower extremities (~25%) and upper extremities (~12% - 16%). This was manifested during isometric contractions as well as during isokinetic contractions. Also, the fatigue index as measured during repeated isometric contractions was consistently higher in patients treated with chemotherapy. Meaning those treated with chemotherapy had more fatigue. The study authors noted that no adverse events were reported as a result of the testing.

Kakinuma *et al.* [5] examined the effects of cytotoxic chemotherapy vs. molecular targeted therapy. There were 44 patients treated with cytotoxic chemotherapy and 21 received molecular targeted therapy. The loss of muscle mass was significantly higher in the cytotoxic chemotherapy group than in the molecular targeted group. This was a 2.19 fold greater loss of muscle mass in the cytotoxic chemotherapy group than the molecular targeted group. The molecular based therapy targeted the epidermal growth factor receptor and the other was an ALK tyrosine kininase inhibitor.

In Sprague-Dawley rats, data from the Dickinson lab [6] suggest that doxyrubicin administration in healthy rats results in a reduction in muscle mass of 26 and 33% in the soleus and EDL muscles, respectively. This is accompanied by a 39 and 35 percent reduction in satellite cells in these muscles. Doxyrubicin was administered at 4 mg/kg with a cumulative dose of 12 mg/kg.

Antoun *et al.* [7] from Dr. Baracos' lab has ascertained that sarcopenia (the

age related loss of muscle mass) in cancer patients results in dose limiting toxicity-meaning that lower doses of chemotherapy must be used in cancer patients with sarcopenia. These investigators reported that in patients with metastatic renal carcinoma with low muscle mass and a BMI less than 25 kg/m^2 there was statistically significant toxicity to sofranib. In a subsequent study, Ali *et al.* [8] from Dr. Baracos group again found, in individuals with cancer, that when they had low lean body mass they had a higher toxicity to chemotherapy. This investigation and the former one discussed from Dr. Baracos lab suggest that it is better to prescribe chemotherapy based on the amount of lean body mass rather on the amount of body surface area. In a study on Japanese cancer patients, Miyamato *et al.*, [9] sarcopenia lead to a poorer prognosis in patients with colorectal cancer who had curative resection. A question that arises, "are chemotherapy drugs metabolized by skeletal muscle"? This may be indicated by the close relationship between amount of skeletal muscle mass and toxicity to chemotherapy found by Dr. Baracos' group.

4. Effect of Resistance Training on Muscle Protein Balance

In a seminal study on the effects of resistance training on muscle protein synthesis, muscle protein breakdown and net muscle protein balance, Phillips *et al.* [10] reported in eight untrained subjects free of disease that muscle protein synthesis after 8 sets of 8 repetitions of the quadriceps femoris muscle group was elevated by 112% three hours after exercise, 65% 24 h after exercise and 34% 48 h after exercise. This was in the fasted condition ie. without post exercise nutrition. This was accompanied by much smaller increases in muscle protein breakdown at 3 and 24 h and a return to baseline at 48 h after exercise. This resulted in a very positive muscle protein synthesis relative to breakdown with the emphasis that this was in fasted condition. This is an important study illustrating the powerful effects of resistance training without feeding on muscle protein synthesis.

In addition, to the powerful effects of resistance training alone, the addition of proper nutrition in the hours and days following a resistance training bout augment the effects of resistance training in the fasted condition. This has been thoroughly reviewed by Stuart Phillips [11]. To summarize these findings predominately from the laboratories of Robert Wolfe and Stuart Phillips ingestion of protein (whey protein is the best), essential amino acids, and leucine are effective in stimulating muscle protein synthesis and net muscle accretion. Phillips *et al.* [11] concluded that 0.25 - 0.3 g/kg body mass/meal is the appropriate amount to ingest in the hours and days post exercise.

Although to this author's knowledge the effects of resistance training, optimal protein/amino acid nutrition, and testosterone administration have not been studied in a composite study, two long-term investigations examining muscle mass and strength suggest that testosterone administration with resistance training are advantageous for gaining muscle and losing fat and if the effective dose is high enough will improve strength also. Hildreth *et al.* [12] administered testosterone gel to elderly subjects and their testosterone concentration reached ap-

proximately 500 - 600 ng/dl. In this study, although they saw a reduction in fat and increase in lean body mass there was no effect on strength. In a subsequent study by Ghandaghi *et al.* [13] reported that testosterone administration with resistance exercise to elderly men by way of injection of Sustanon (250 mg biweekly) raised the testosterone of men with normal testosterone to approximately 1000 - 1200 ng/dl resulted in an increase in lean body mass, a decrease in fat mass, AND an increase in strength. It would appear that the increase in strength is related to the relatively higher testosterone concentrations achieved in the study of Ghandaghi *et al.* [13]. The study of Hildreth *et al.* [12] lasted 6 months whereas the study of Gharahdaghi *et al.* [13] lasted 6 weeks.

5. Effect of Resistance Training with Testosterone and Megestrol Acetate Administration on Muscle Mass

In an effort to have older underweight men accrue muscle mass we [14] administered the appetite stimulant megestrol acetate, the anabolic agent testosterone, and the anabolic intervention whole body resistance training. As can be seen in **Figure 1**, megestrol acetate alone induced muscle mass loss which was not attenuated by testosterone administration.

Resistance exercise with megestrol acetate administration resulted in a total attenuation of muscle mass loss and the addition of testosterone administration to megestrol acetate and whole body resistance training administration resulted in a substantial gain in thigh muscle mass (bars 2 and 4). We hypothesized that megestrol acetate blocked the androgen receptor making testosterone alone incapable of increasing muscle mass and that in someway resistance training stopped this effect and when combined with testosterone replacement and megestrol acetate administration resulted in a substantial increase in muscle mass.

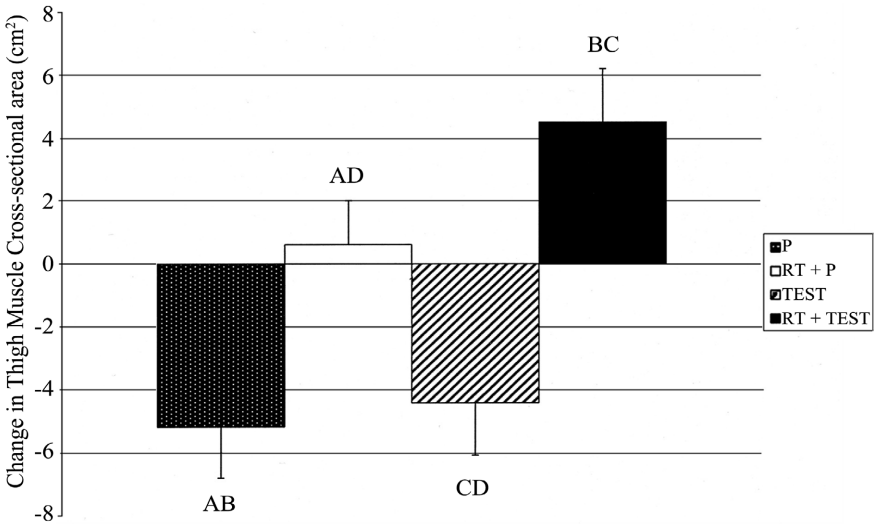

Figure 1. Effects of Megestrol Acetate, Megestrol Acetate plus Resistance Training, Megestrol Acetate plus Testosterone, and Megestrol Acetate plus Resistance Training plus Testosterone on thigh cross-sectional Muscle Mass, bars above from left to right, respectively. From [14].

6. Effect of Resistance Training on Monocyte Cytokine Secretion and Toll Like Receptor-4 Content

Most of this seminal work comes from the laboratory of Dr. Michael Flynn when he was at Purdue University. In essence Dr. Flynn's group has shown that resistance exercise *acutely* (a single bout/ expressed per monocyte) acts to reduce lipopolysaccharide induced secretion of IL-1Beta and TNF alpha in vitro from whole blood taken from human volunteers [15] immediately post and 2 hours post exercise. Also, Dr. Flynn's group has shown cross-sectionally that resistance exercise training reduces LPS-stimulated TNFalpha and IL-6 production in vitro [16]. This cross-sectional finding was also shown to occur prospectively as this group [17] reported resistance exercise training (10 weeks) reduced TNFalpha by 37% as well as LPS-stimulated production of IL-6, IL1-beta, and TNFalpha at all time points including the pre time point.

The so-called gate keeper for monocyte cytokine production is Toll Like Receptor-4 which has to be stimulated for cytokines to be produced by the monocyte. These investigators found that TLR-4 was reduced as a result of resistance exercise training (the mRNA) in older women [18]. This provides a mechanism for the reduction in IL-6, TNFalpha, and IL-1Beta seen with chronic resistance training. Regarding skeletal muscle rather than blood monocyte cytokine production, Lambert *et al.* [19] reported that the mRNA for TLR-4 in skeletal muscle was significantly reduced as a result of resistance and aerobic exercise training but this effect did not happen as a result of energy restriction. Taken together the results from Flynn *et al.* laboratory [15] [16] [17] [18] and that reported by Lambert *et al.* [19] suggest that resistance training, in particular, may be effective from an immunological standpoint, in reducing muscle catabolism in healthy individuals. The effects of this intervention on this immunological parameters needs to be determined in cancer cachexia and logically we can speculate that positive results would be observed in cancer patient. This awaits scientific corroboration. Interestingly, Paccielli-Freire [20] reported that in pancreatic cancer tumors the expression of cachexia inducing factor genes appeared to be coming from leukocytes which infiltrated the tumor microenvironment rather than from the tumor itself. Additionally, there was no statistical relationship between cachexia inducing factor gene expression and tumor grade.

7. Effect of Resistance Training in the Face of Physical Frailty and Negative Energy Balance on Muscle Anabolism

In two separate studies it would appear that physical frailty and negative energy balance-two maladies present in cancer cachexia—do not inhibit the effects of resistance training on body composition and strength. In the first study, Villareal *et al.* [21] reported that a multicomponent exercise program which utilized balance, flexibility, strength training, and aerobic training decreased fat mass and increased overall lean body mass, lean body mass of the limbs, overall strength and aerobic fitness level (VO2peak). This was performed in 65 - 80 year old frail

and obese men and women. This could be considered somewhat of a proof of concept study for cancer cachexia as the volunteers were frail.

In another study which utilized older individuals, Murphy *et al.* [22] reported that energy restriction resulted in a blunting of myofibrillar (contractile) protein synthesis whereas there was no effect on myofibrillar protein synthesis when in energy balance. Resistance training while undergoing moderate energy restriction-which is somewhat similar to the anorexia of cancer resulted in a stimulation of myofibrillar muscle protein synthesis. The energy restriction (caloric deficit) was for 4 weeks at −1.25 MJ/day (−~300 kcal/day). This energy restriction is fairly small compared to the anorexia of cancer [23]. Nonetheless, the data do show that protein synthesis can be stimulated if resistance exercise is undertaken and there is moderate energy restriction *i.e.* weight loss.

8. Effect of Resistance Training in Cancer on Lean Body Mass and Muscle Strength

Santagnello *et al.* [24] reported that 12 weeks of resistance training reduced self reported fatigue, increased muscle power, lean body mass and walking speed performance, sit to stand time, and timed get up and go in cancer patients. Serra *et al.* [25] reported that 16 weeks of moderate intensity resistance training (whole body) improved muscle strength by about 25% - 30%, and quality of life by about 10%. Measures of physical function such as chair stand time was improved by 15% and six minute walk time was improved by 4%. Fatigue was reduced by 58%. The population studied was breast cancer survivors. Wiskemann *et al.* [26], reported in 65 patients with breast cancer, that resistance training, either supervised or home-based, 2 times per week resulted in a significant increase in strength only in the unsupervised group for elbow flexors and extensors and knee extensors.

9. Discussion

It is clear that cancer and chemotherapy result in a loss of muscle mass and this could be a cause of death in a large number of cancer patients. Resistance exercise would appear to be a viable intervention from the standpoint of increasing muscle protein synthesis [10] and allowing for the accrual of muscle mass. By partaking in resistance training, the ability to retain muscle mass would appear to be significantly impacted. The positive benefit of resistance training is also enhanced, in individuals without cancer, with proper post exercise nutrition and testosterone administration. These interventions together would likely improve lean body mass retention, strength, and physical function in the cancer patient. One question that arises is what energy cost of such activity and it would appear that the type of resistance training we are talking about [for example: 10 exercises/3 sets of 8 @ 70% - 80% of the one repetition maximum and 3 times per week would not expend a substantial amount of calories-on the order of about ~200 kcals [27]. With regard to the anorexia of cancer, the addition of the appetite

stimulant megestrol acetate with resistance training and testosterone administration has led to significant weight gain and muscle mass gains [14]. Anamorelin, a ghrelin analogue and growth hormone secretagogue has been shown to improve appetite and lead to lean body mass accrual [2]. The mechanism by which resistance training could impact muscle mass is likely through a direct effect on muscle protein synthesis [10], however, the seminal work of Flynn et als laboratory [15] [16] [17] [18] suggests that downregulating proinflammatory cytokine production could be another putative mechanism by which resistance exercise could reduce the catabolic effects of cancer.

10. Conclusion

It is clear that cancer causes muscle wasting and this may be the cause of death in many cancer patients [1]. Chemotherapy may add to the catabolic effects of cancer [6]. From the work of Baracos *et al.* [7] [8], it appears that measures of fat free mass/lean body mass/muscle mass may be of more precise in the calculation of chemotherapy dosage than the use of body surface area. Resistance exercise increases muscle protein synthesis and the addition of muscle mass in normal individuals without cancer. This mode of exercise is even more effective when proper nutrition and anabolic therapies, such as testosterone administration are undertaken [12] [13]. To this end, having a sufficiently high (high-normal range) testosterone concentration would appear to be optimal for a strong effect on fat free mass and ultimately an effect on function [13]. The positive benefits of resistance exercise would appear to be via an improvement in muscle protein synthesis [10], however, this could be precluded by a decrease in proinflammatory cytokines as has been shown by Flynn's group in normal elderly individuals free of disease [15] [16] [17] [18]. The utility of resistance training has been substantiated in the frail-obese elderly [21] and individuals who are hypocalorically dieting [22] thus the potential to be of great usefulness in cancer cachexia is probable. Preliminary investigations in cancer patients have shown beneficial results in these patient groups [24] [25] [26].

11. Future Directions

From the review above, a few pertinent future directions can be put forth. First, it is the opinion of these authors that whole body methods utilizing MRI, CT, or DEXA scans or non-radiological methods such as total body water determination or other dilution techniques at the whole body level should be utilized rather a CT scan at the third lumbar vertebrae.

A second future endeavor may be to utilize muscle mass or a close surrogate such as fat free mass or lean body mass to estimate chemotherapy dosage. Data from Dr. Baracos' lab [7] [8] suggest that a toxicity to chemotherapy is highly related to muscle mass and therefore should be used for the calculation of chemotherapy dosage rather than total body surface area.

Clearly, studies on muscle protein synthesis and breakdown as a result of re-

sistance training must be conducted in cancer patients to confirm the utility of this practice in this disease population.

Optimal enteral or parenteral nutrition for the cancer patient who undergoes resistance training is important for the different types and sizes of tumors encountered as well as well as when metasteses are present.

Research on the role of the immune system and resistance exercise in cancer patients is warranted but the outlook appears positive based on the results in individuals free of disease.

The dose response relationship of resistance training and muscle mass retention in cancer patients needs to be determined with the idea of doing the minimal amount of work to maintain muscle mass and not compromise the immune system being the goal.

Finally, a "Gym" or a room for resistance training equipment that a cancer patient could walk to, or have their bed wheeled to, in a hospital setting, would appear to be a viable solution to potential logistical problem.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Argiles, J.M., Busquets, S., Stemmler, B. and Lopez-Soriano, F.J. (2014) Cancer Cachexia: Understanding the Molecular Basis. *Nature Reviews Cancer*, **14**, 754-762. https://doi.org/10.1038/nrc3829

[2] Lambert, C. (2021) Attenuating Cancer Cachexia-Prolonging Life. In: D'Onofrio, G. and Cseri, J., Eds., *Frailty and Sarcopenia-Recent Evidence and New Perspectives*, IntechOpen, London.

[3] Blauwhoff-Buskermolen, S., Versteeg, K.S., de van der Schueren, M.A., den Braver, N.R., Berkhof, J., Langius, J.A., *et al.* (2016) Loss of Muscle Mass during Chemotherapy Is Predictive for Poor Survival of Patients with Metastatic Colorectal Cancer. *Journal of Clinical Oncology*, **34**, 1339-1344. https://doi.org/10.1200/JCO.2015.63.6043

[4] Klassen, O., Schmidt, M.E., Ulrich, C.M., Schneeweiss, A., Potthoff, K., Steindorf, K., *et al.* (2017) Muscle Strength in Breast Cancer Patients Receiving Different Treatment Regimes. *Journal of Cachexia, Sarcopenia and Muscle*, **8**, 305-316. https://doi.org/10.1002/jcsm.12165

[5] Kakinuma, K., Tsuruoka, H., Morikawa, K., Furuya, N., Inoue, T., Miyazawa, T., *et al.* (2018) Differences in Skeletal Muscle Loss Caused by Cytotoxic Chemotherapy and Molecular Targeted Therapy in Patients with Advanced Non-Small Cell Lung Cancer. *Thoracic Cancer*, **9**, 99-104. https://doi.org/10.1111/1759-7714.12545

[6] D'Lugos, A.C., Fry, C.S., Ormsby, J.C., Sweeney, K.R., Brightwell, C.R., Hale, T.M., *et al.* (2019) Chronic Doxorubicin Administration Impacts Satellite Cell and Capillary Abundance in a Muscle-Specific Manner. *Physiological Reports*, **7**, e14052. https://doi.org/10.14814/phy2.14052

[7] Antoun, S., Baracos, V.E., Birdsell, L., Escudier, B. and Sawyer, M.B. (2010) Low Body Mass Index and Sarcopenia Associated with Dose-Limiting Toxicity of Sora-

fenib in Patients with Renal Cell Carcinoma. *Annals of Oncology*, **21**, 1594-1598. https://doi.org/10.1093/annonc/mdp605

[8] Ali, R., Baracos, V.E., Sawyer, M.B., Bianchi, L., Roberts, S., Assenat, E., *et al.* (2016) Lean Body Mass as an Independent Determinant of Dose-Limiting Toxicity and Neuropathy in Patients with Colon Cancer Treated with FOLFOX Regimens. *Cancer Medicine*, **5**, 607-616. https://doi.org/10.1002/cam4.621

[9] Miyamoto, Y., Baba, Y., Sakamoto, Y., Ohuchi, M., Tokunaga, R., Kurashige, J., *et al.* (2015) Sarcopenia Is a Negative Prognostic Factor after Curative Resection of Colorectal Cancer. *Annals of Surgical Oncology*, **22**, 2663-2668. https://doi.org/10.1245/s10434-014-4281-6

[10] Phillips, S.M., Tipton, K.D., Aarsland, A., Wolf, S.E. and Wolfe, R.R. (1997) Mixed Muscle Protein Synthesis and Breakdown after Resistance Exercise in Humans. *American Journal of Physiology*, **273**, E99-E107. https://doi.org/10.1152/ajpendo.1997.273.1.E99

[11] Phillips, S.M. (2014) A Brief Review of Critical Processes in Exercise-Induced Muscular Hypertrophy. *Sports Medicine*, **44**, S71-S77. https://doi.org/10.1007/s40279-014-0152-3

[12] Hildreth, K.L., Barry, D.W., Moreau, K.L., Vande Griend, J., Meacham, R.B., Nakamura, T., *et al.* (2013) Effects of Testosterone and Progressive Resistance Exercise in Healthy, Highly Functioning Older Men with Low-Normal Testosterone Levels. *The Journal of Clinical Endocrinology and Metabolism*, **98**, 1891-1900. https://doi.org/10.1210/jc.2012-3695

[13] Gharahdaghi, N., Rudrappa, S., Brook, M.S., Idris, I., Crossland, H., Hamrock, C., *et al.* (2019) Testosterone Therapy Induces Molecular Programming Augmenting Physiological Adaptations to Resistance Exercise in Older Men. *Journal of Cachexia, Sarcopenia and Muscle*, **10**, 1276-1294. https://doi.org/10.1002/jcsm.12472

[14] Lambert, C.P., Sullivan, D.H., Freeling, S.A., Lindquist, D.M. and Evans, W.J. (2002) Effects of Testosterone Replacement and/or Resistance Exercise on the Composition of Megestrol Acetate Stimulated Weight Gain in Elderly Men: A Randomized Controlled Trial. *The Journal of Clinical Endocrinology and Metabolism*, **87**, 2100-2106. https://doi.org/10.1210/jcem.87.5.8505

[15] Phillips, M.D., Flynn, M.G., McFarlin, B.K., Stewart, L.K., Timmerman, K.L. and Ji, H. (2008) Resistive Exercise Blunts LPS-Stimulated TNF-Alpha and Il-1 Beta. *International Journal of Sports Medicine*, **29**, 102-109. https://doi.org/10.1055/s-2007-965115

[16] Markofski, M.M., Flynn, M.G., Carrillo, A.E., Armstrong, C.L., Campbell, W.W. and Sedlock, D.A. (2014) Resistance Exercise Training-Induced Decrease in Circulating Inflammatory CD14+CD16+ Monocyte Percentage without Weight Loss in Older Adults. *European Journal of Applied Physiology*, **114**, 1737-1748. https://doi.org/10.1007/s00421-014-2902-1

[17] Phillips, M.D., Flynn, M.G., McFarlin, B.K., Stewart, L.K. and Timmerman, K.L. (2010) Resistance Training at Eight-Repetition Maximum Reduces the Inflammatory Milieu in Elderly Women. *Medicine & Science in Sports & Exercise*, **42**, 314-325. https://doi.org/10.1249/MSS.0b013e3181b11ab7

[18] Phillips, M.D., Patrizi, R.M., Cheek, D.J., Wooten, J.S., Barbee, J.J. and Mitchell, J.B. (2012) Resistance Training Reduces Subclinical Inflammation in Obese, Postmenopausal Women. *Medicine & Science in Sports & Exercise*, **44**, 2099-2110. https://doi.org/10.1249/MSS.0b013e3182644984

[19] Lambert, C.P., Wright, N.R., Finck, B.N. and Villareal, D.T. (2008) Exercise but Not

Diet-Induced Weight Loss Decreases Skeletal Muscle Inflammatory Gene Expression in Frail Obese Elderly Persons. *Journal of Applied Physiology* (1985), **105**, 473-478. https://doi.org/10.1152/japplphysiol.00006.2008

[20] Freire, P.P., Fernandez, G.J., de Moraes, D., Cury, S.S., Dal Pai-Silva, M., Dos Reis, P.P., *et al.* (2020) The Expression Landscape of Cachexia-Inducing Factors in Human Cancers. *Journal of Cachexia, Sarcopenia and Muscle*, **11**, 947-961. https://doi.org/10.1002/jcsm.12565

[21] Villareal, D.T., Smith, G.I., Sinacore, D.R., Shah, K. and Mittendorfer, B. (2011) Regular Multicomponent Exercise Increases Physical Fitness and Muscle Protein Anabolism in Frail, Obese, Older Adults. *Obesity* (*Silver Spring*), **19**, 312-318. https://doi.org/10.1038/oby.2010.110

[22] Murphy, C.H., Churchward-Venne, T.A., Mitchell, C.J., Kolar, N.M., Kassis, A., Karagounis, L.G., *et al.* (2015) Hypoenergetic Diet-Induced Reductions in Myofibrillar Protein Synthesis Are Restored with Resistance Training and Balanced Daily Protein Ingestion in Older Men. *American Journal of Physiology-Endocrinology and Metabolism*, **308**, E734-E743. https://doi.org/10.1152/ajpendo.00550.2014

[23] Graf, S.A. and Garcia, J.M. (2017) Anamorelin Hydrochloride in the Treatment of Cancer Anorexia-Cachexia Syndrome: Design, Development, and Potential Place in Therapy. *Drug Design, Development and Therapy*, **11**, 2325-2331. https://doi.org/10.2147/DDDT.S110131

[24] Santagnello, S.B., Martins, F.M., de Oliveira Junior, G.N., de Freitas Rodrigues de Sousa, J., Nomelini, R.S., Murta, E.F.C., *et al.* (2020) Improvements in Muscle Strength, Power, and Size and Self-Reported Fatigue as Mediators of the Effect of Resistance Exercise on Physical Performance Breast Cancer Survivor Women: A Randomized Controlled Trial. *Support Care Cancer*, **28**, 6075-6084. https://doi.org/10.1007/s00520-020-05429-6

[25] Serra, M.C., Ryan, A.S., Ortmeyer, H.K., Addison, O. and Goldberg, A.P. (2018) Resistance Training Reduces Inflammation and Fatigue and Improves Physical Function in Older Breast Cancer Survivors. *Menopause*, **25**, 211-216. https://doi.org/10.1097/GME.0000000000000969

[26] Wiskemann, J., Clauss, D., Tjaden, C., Hackert, T., Schneider, L., Ulrich, C.M., *et al.* (2019) Progressive Resistance Training to Impact Physical Fitness and Body Weight in Pancreatic Cancer Patients: A Randomized Controlled Trial. *Pancreas*, **48**, 257-266. https://doi.org/10.1097/MPA.0000000000001221

[27] Phillips, W.T. and Ziuraitis, J.R. (2003) Energy Cost of the ACSM Single-Set Resistance Training Protocol. *The Journal of Strength & Conditioning Research*, **17**, 350-355. https://doi.org/10.1519/00124278-200305000-00023