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Issues in Nutrition and Cancer: UPDATE 2004

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Issues in Nutrition and Cancer: An Overview for Clinicians

by Faith D. Ottery, MD, PhD

…an increasing number of cancer survivors are living with long-term effects of disease and treatment that impair their functioning and quality of life. While diagnosis, treatment, and even cure-oriented research continues, it is imperative that there be a parallel commitment to the improvement of the status of everyday living for cancer survivors. Development of research-based clinical interventions in these areas holds promise for significant improvement in functioning and quality of life for cancer survivors and may constitute valuable rehabilitation techniques that can be adjunctive to standard therapies.[1]

—Maryl Winningham, RN, PhD

When I was asked to coordinate this supplement to address the inclusion of the principles and practice of nutritional oncology into an integrated approach to cancer care, I was particularly honored since the supplement is to be published on the celebration of the 30th anniversary of the Association of Community Cancer Centers (ACCC). Dr. Winningham's comments echo components of ACCC's Mission: to preserve and protect the entire continuum of quality cancer care.[2]

Standardization of assessment and evidence-based clinical interventions are imperative to optimize patient functionality and quality of life across the cancer experience. In the following articles, we applied a framework, defined by Courneya and colleagues,[3] for physical exercise across the cancer experience to the broader concepts of functionality and quality of life (Figure 1). Known as the "Framework PEACE" (Physical Exercise Across the Cancer Experience), this proposed framework divides the cancer experience into six time periods: two prediagnosis (prescreening and screening/diagnosis), and four postdiagnosis (pretreatment, treatment, posttreatment, and resumption).[3] As with the original concept, it is hoped that this framework will stimulate a more comprehensive and in-depth inquiry into the role of functionality and quality of life in cancer control.

QUALITY OF SURVIVORSHIP AND NUTRITION

With the successes in cancer diagnosis and treatment accomplished over the past 70-plus years, we have a growing population of cancer survivors. Quality of survivorship is important, whether we are talking about the four postdiagnosis periods for a given survivor or the two prediagnosis periods for the family members who want and need to address aspects of lifestyle as they affect risks for developing cancer, as well as the prognosis of that cancer should it develop.

For many people, quality of survivorship is as important as the duration of survivorship, whether one is addressing *acute* (e.g., having enough energy to go out and get the morning paper), *intermediate* (e.g., getting back to work or usual activity) or *chronic* time frames (e.g., chronic sequelae of body composition loss and fatigue years after completion of therapy as in lymphoma[4] or lung cancer[5]). In addition, it can be postulated that those patients who maintain better nutritional status and body composition during and after primary therapy are better and more willing candidates for therapy should the cancer recur.

PREVENTION, PHYSICAL ACTIVITY, AND HEALTH

Cancer is a disease process that affects not only the individual patient but also his or her family members and significant others. Often when a parent is diagnosed with a cancer, the question is asked, "What can we do so that my daughter/son doesn't have to go through this?" Any answer to questions about what one can do to prevent cancer or improve prognosis must include a discussion about the components of nutrition and physical activity, with the goal of optimizing body composition and metabolism. While we do not specifically address the issues of nutrition and exercise in cancer prevention in any of the following articles, the discussion of this quality of survivorship would be incomplete without a brief summary of what is known about nutrition, exercise, and body composition in terms of cancer risk and prognosis.

The proposed Health Determinants and Health Outcomes Set of the Healthy People 2010[6] program includes eight indicators representative of health determinants: physical environment, poverty, high school graduation, tobacco use, weight, physical activity, health insurance, and cancer detection. These indicators have been chosen because they represent some of the most powerful determinants of health for which meaningful action can be taken at multiple jurisdictional levels, ranging from the national and state levels to individuals and families in neighborhoods and communities.

Two indicators address health outcomes. The first focuses on prevention of mortality associated with intentional and unintentional injuries, while the second addresses the extent to which illness, injury, or disability prevents people from performing important social roles. The

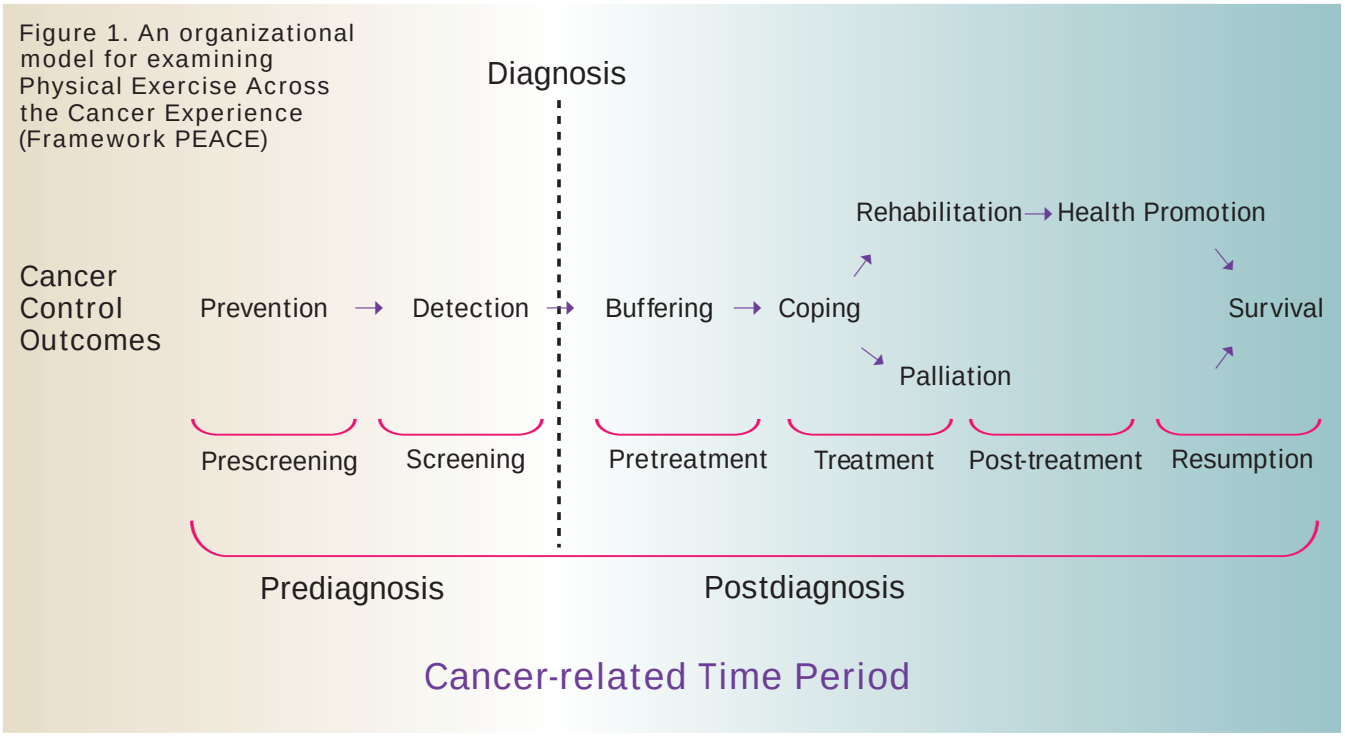

Figure 1. An organizational model for examining Physical Exercise Across the Cancer Experience (Framework PEACE)

indicator set, therefore, recognizes that just as society has an effect on health, so too the health of the population has an effect on the functioning and productivity of society.

Since the 1940s body weight, body fat distribution, and adult weight gain have been linked to the development of endometrial, postmenopausal breast, colon, esophageal, and renal carcinoma incidence and breast carcinoma prognosis.[7-9] Studies also point to a possible role for physical activity in cancer incidence, because of the interrelationship between weight and physical activity. Considerable data indicate a 40 to 50 percent reduction in colon carcinoma incidence in active compared to sedentary individuals and a 30 to 40 percent reduction in breast carcinoma incidence among women engaging in three or more hours per week of regular vigorous activity. Somewhat more limited and less consistent data associate prostate and lung carcinoma with inactivity.[7, 10,11]

In the context of the growing interest in "metabolic syndrome" or hyperinsulinemia as a determinant of compromised health in terms of obesity, type II diabetes mellitus, and cardiovascular risk, data now suggest a role for this syndrome in risk for breast, colorectal, and prostate cancer and for their prognosis.[12-18] Current evidence suggests that obesity, lack of physical activity, alcohol consumption, and a typical high-energy Western diet are all associated with the development of insulin resistance and hyperinsulinemia and may stimulate the growth of tumors, particularly breast and colorectal tumors.[12,14-16,19] Hyperinsulinemia has also been associated with mortality in breast cancer patients.[20] Elevated waist-to-hip ratio, representing a higher abdominal fat distribution, is a marker of insulin resistance and hyperinsulinemia[22,23] and has been associated with both incidence of and mortality of several chronic diseases, including heart disease, hypertension, diabetes mellitus, and cancer.[24-26]

The articles that compose this supplement address areas of clinical importance in caring for cancer survivors—from those undergoing current therapy to those for whom chemotherapy or radiation are somewhat distant memories. The topics discussed in the following articles are part of the "food for thought" as ACCC celebrates its 30th Anniversary and clearly support the mission statement and the vision that form the foundation of the Association.

Faith D. Ottery, MD, PhD, is the founding president of the Society for Nutritional Oncology Adjuvant Therapy (NOAT) and current chair of the Rehabilitation Committee of the Multinational Association of Supportive Care in Cancer (MASCC). Her research focuses on the complex interplay of nutrition and exercise that forms the basis of many of the seminal publications in the field of nutritional oncology. She trained in medical oncology and was a practicing surgical oncologist at Fox Chase Cancer Center from 1987-1994. She is director of medical affairs in oncology, HIV, and geriatrics for Savient Pharmaceuticals, Inc.

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New Approaches in Reversing Cancer-related Weight Loss

by Vickie E. Baracos, PhD

IN BRIEF

Should those of us involved in anticancer therapy of patients adopt the mindset of our sports medicine colleagues? The few available trials suggest that in cancer patients, resistance training, adequate protein, and amino acid or amino acid derivative supplementation can each individually promote net gain of lean body mass and associated function. If these observations are borne out, it seems possible to conjecture that a combination therapy involving several or all of these may hold the promise of much more important gains—as seen in healthy people.

Cancer cachexia is a profound metabolic process characterized by the breakdown of skeletal muscle, as well as abnormalities in fat and carbohydrate metabolism. The diagnosis of cachexia is made by a history of substantial weight loss in the context of advanced disease and a physical examination demonstrating muscle wasting. The prognostic significance of weight loss in cancer patients is well established, with weight loss strongly associated with shortened survival and poor response to therapy from the earliest disease stages through to advanced cancer. The negative nitrogen balance underlying cancer cachexia leads to a significant wasting of skeletal muscle and other lean tissues. This lean tissue loss reduces patient mobility, jeopardizes respiratory function, is related to reduced immunity, and is associated with poor performance status and outcome. Stabilizing muscle loss or regaining lean tissue mass must, therefore, be considered primary targets of cachexia therapy.

Research on the biology of skeletal muscle and its regulatory anabolic and catabolic factors is many decades old. Skeletal muscle is terminally differentiated. Thus, it is not cell division and cell death that contribute to muscle mass, but mainly synthesis and degradation of proteins within existing cells. These metabolic processes have been described in considerable biochemical detail and are known to be precisely controlled.

A host of factors stimulating muscle protein synthesis and degradation has been characterized. These fall into three major categories: muscular work/mechanical activity, endocrine factors, and nutrients. Muscle mass and function are dependent on this simple triad. In any given person and within any given physiological state, these three categories of influences combine to define muscle mass. A fourth category of stimuli exists: a series of catabolic factors that mainly occur during disease or injury, including tumor-derived factors.[1]

FACTORS INFLUENCING MUSCLE LOSS AND GAIN

The plasticity of skeletal muscle—its ability to adapt—covers a broad range.

Muscle mass falls to a minimum when:

- Contractile work is limited or absent
- Nutrients (especially amino acids for building muscle protein and necessary co-factors) are unavailable
- Anabolic hormones, such as insulin and testosterone, are at low levels or when muscle is resistant to their action
- Catabolic factors related to stress (i.e., cortisol) or disease (i.e., proinflammatory cytokines) are present.

Muscle mass rises to its maximum when:

- Contractile work is frequent, especially resistance-type activity (i.e., weight-lifting)
- Nutrients (especially amino acids for building muscle protein and necessary co-factors) are not limiting
- Anabolic hormones, such as insulin and testosterone, are at optimal levels and muscle is sensitized to their action
- Catabolic factors related to stress (i.e., cortisol) or disease (i.e., proinflammatory cytokines) are absent.

ANABOLIC COMPETENCE—THE SPORTS MEDICINE APPROACH

The commonly used approach in sports for building maximal muscle mass is well known: resistance training (weight-lifting); nutritional supplements, especially protein; and a variety of natural and synthetic hormones to provide the three strong anabolic signals to which muscles can respond. These signals are synergistic, not just additive in their action, which can lead to spectacular gains of muscle in some individuals. While some of the interventions have been controversial, the model does demonstrate the importance of integrating the approaches.

The approach used in sports training is highly developed. Detailed progressive weight-training programs, addressing specific muscle groups are available in any sports training manual, as well as in physical therapy texts. The amino acid requirements for maximal muscle growth are at least partially understood, and these are commercially available as amino acid and protein supple-

Integrated Interventions in Nutritional Oncology

The goal of nutritional intervention in patients with cancer is to prevent or reverse the progressive weight loss and inanition that is seen in up to 80 percent of patients at some point in their disease or treatment. Unfortunately, even this simple goal is rarely achieved, and there has been little or no progress in impacting the gold standard of survival by simply addressing nutritional interventions. Clinicians who use nutritional therapies alone to combat weight loss in cancer patients experience three common frustrations: 1) lack of consistent reversal of weight loss with intervention, 2) lack of repletion of lean tissue or muscle, and 3) lack of translation of any change in weight or nutritional parameters into improved oncology outcomes.

This relative lack of success can be presumed to be because of a one-dimensional approach that does not integrate nutrition into a program of comprehensive cancer care. A paradigm of integrated intervention has been developed that supports anabolism or anabolic competence, defined as that state which optimally supports protein synthesis and lean body mass.[1] This paradigm also addresses the more global problems of muscle and organ function, immune competence, functionality, and quality of life. This approach is illustrated in Figure 1 and demonstrates the importance of addressing the three primary components of intervention: nutrition, the hormonal milieu (including both classic hormones and cytokines), and exercise.

Until recently, treatment of cancer cachexia has focused on the provision of macro- and micronutrients to reverse weight loss, with little clinical attention to the composition of body tissues lost or repleted. During the past decade, the level of understanding of the etiology of muscle catabolism in cancer cachexia, as well as intermediary markers of muscle breakdown and lipid mobilization, have served to re-focus research into interventional options for cancer cachexia that target the functional aspects of body composition (lean tissue)—instead of simply focusing on energy reserves (adipose tissue). This appreciation is addressed by Vicki Baracos, PhD. A more comprehensive review of the understanding and management of cancer cachexia has recently been published by Baracos and her colleagues in Canada.[2]

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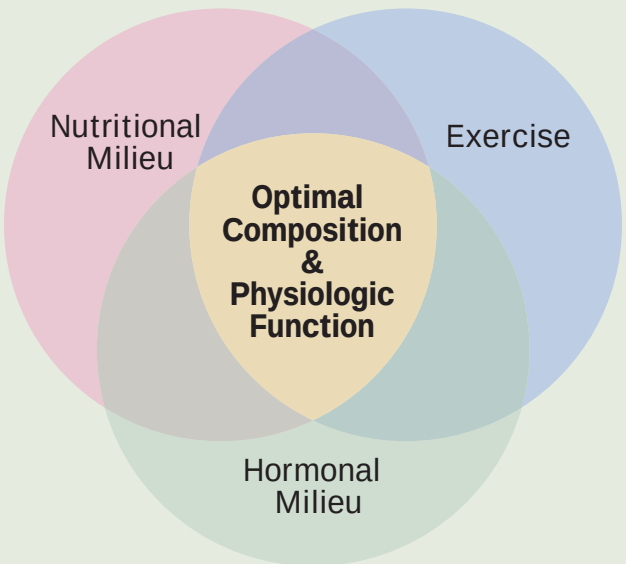
Figure 1. The Three Primary Components of Nutritional Intervention



ments in various combinations and forms. While these were initially used based on anecdotal evidence, there is an increased research database supporting the use of some and refuting others. Elegant work has been done on the appropriate timing of protein feeding, relative to the timing and type of exercise bouts.[2] Synthetic anabolic steroids derived and developed from the basic structure of testosterone have been intensified in their anabolic action on skeletal muscle, while minimizing other effects, such as liver damage and male pattern hair growth.[3,4] Creatine supplementation in the diet is used as an adjunct in this recipe, as creatine phosphate serves as an essential phosphate donor for the synthesis of ATP, a critical energy source for initiating muscle activity.[5-17]

Evidence of the success of this integrated muscle-building program can be seen in gymnasiums, bodybuilding competitions, and football fields. The sports model is simple, and—insofar as it involves diet and activity—can be generally inexpensive and can be used by patients directly or coordinated by the clinician. Use of pharmaco-

logic intervention, such as anabolic agents, is to be regarded as a medical intervention, with appropriate dosing and monitoring in the context of the underlying disease.

APPLYING THE SPORTS MEDICINE MODEL TO PATIENTS WITH WASTING SYNDROMES

Fatigue is the most distressing phenomenon experienced by cancer patients.[18] Vogelzang and colleagues used a survey designed to characterize the epidemiology of cancer-related fatigue from the perspectives of the patient (n = 419, median age 65), primary caregiver (n = 200), and oncologist (n = 197).[18] The principal cancer diagnoses were breast in females and genitourinary in males. Cancer treatment included chemotherapy (59 percent), radiation therapy (63 percent), or both (24 percent); 20 percent of patients received their last treatment within 6 weeks, 31 percent within 7 to 52 weeks, and 49 percent more than one year ago.

More than three-fourths of patients (78 percent) experienced fatigue, defined as a general feeling of debilitating tiredness or loss of energy, during the course of their disease and treatment, 32 percent daily, and 32 percent reported fatigue significantly affecting their daily routines. Caregivers reported observing fatigue in 86 percent of the index patients, and oncologists perceived that 76 percent of their patients experienced fatigue. Patients felt that fatigue adversely affected their daily lives more than pain (61 percent vs. 19 percent). Most oncologists (80 percent) believed fatigue is overlooked or undertreated, and most patients (74 percent) considered fatigue a symptom to be endured. Fifty percent of patients did not discuss treatment options with their oncologists, and only 27 percent reported that their oncologists recommended any treatment for fatigue.

Given this background, it is important to consider that fatigue is multifactorial in etiology. However, the significant catabolic loss of muscle is an important target for interventional consideration. It is possible to argue that we already have the knowledge necessary to improve muscle mass and consequently patient function and mobility—that is, we know the sports-training approach that results in increased muscle mass. What seems to be lacking is the translation of this knowledge into practice. Are the "new" integrated approaches to supporting anabolism to wasting syndromes simply the application of well-established concepts? Should those of us involved in anticancer therapy of patients adopt the mindset of our sports medicine colleagues? This integrated approach of nutrition, resistance and aerobic exercise, and appropriate hormonal support has already been adopted by researchers in muscle wasting in the elderly,[19-21] in patients with wasting syndromes associated with AIDS,[22,23] and chronic obstructive pulmonary disease.[24-26]

Clinical researchers in cancer cachexia and anorexia can learn from the related research work of their colleagues in other disciplines. Some results from clinical trials looking at reversal of muscle wasting in noncancer disease may be immediately translatable to cancer populations. Research in the sports medicine area has led the way with interventions, including creatine, amino acids, and anabolic agents, in combination with exercise programs tailored to develop muscle mass and optimize performance. Clinical research on wasting in the elderly has a relatively long history and has been the focus of activity in large research centers. AIDS and COPD cachexia research has been enhanced by targeted funding and is also quite active at this time.

RESISTANCE MUSCLE TRAINING TO BUILD MUSCLE MASS AND STRENGTH

Currently literature on exercise training and muscle anabolism is very extensive, and a review of this literature is outside the scope of this article. (See page 11.) However, exercise training is shown clearly to stimulate muscle protein synthesis and to develop muscle mass and functional status. A key point emerging from the research is that our concept of who can exercise should be revisited. Various patients considered too frail and ill to exercise have been shown to benefit from exercise. Schulte and Yarasheski[19] provide a pertinent example in frail elderly (76 to 92 years of age) who participated in up to three months of weightlifting. Study participants showed increased biosynthesis of myosin heavy chain and mixed muscle proteins, as do younger people. This finding suggests that the protein synthetic machinery adapts rapidly to increased contractile activity and that the adaptive responses are maintained, even in frail elders.

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In addition, evidence from recent publications indicates that repeated exercise may enhance the fitness, strength, and quality of life of cancer patients. The studies have addressed patients with a variety of different cancers. In one study, men with prostate cancer who were scheduled to receive androgen deprivation therapy were randomly assigned to an intervention group that participated in a resistance exercise program three times per week for 12 weeks or to a waiting list control group.[27] Men in the resistance intervention group demonstrated fewer fatigue-related problems with

activities of daily living and had a higher quality of life and higher levels of upper-body and lower-body muscular fitness than men in the control group.

Dimeo and coworkers [28] have produced a surprising series of reports on exercise in patients undergoing chemotherapy, including high-dose chemotherapy with stem cell rescue. These patients are generally very sick in the aftermath of chemotherapy, yet they are able and willing to exercise. These daily physical training programs reduce the treatment-related loss of physical performance in patients with hematological malignancies undergoing chemotherapy. The lack of reported negative effects and the consistency of the observed benefits lead to the conclusion that physical exercise may provide a low-risk therapy that can improve patients' capacity to perform activities of daily living and improve their quality of life.[29]

BEYOND EXERCISE: AN INTEGRATED APPROACH

In addition to the exercise interventions that have been studied in patients with cancer, the use of other interventions that may be used by patients needs to be addressed by clinicians caring for patients with cancer. Clinicians should question patients with an open mind regarding any aspect of complementary medicine. If the issue is not raised by the clinician, the patient or family may fail to include the information in any medical review.

Creatine. Creatine is a very commonly-used supplement among athletes who believe creatine builds muscle and increases muscle energy, enabling them to train longer and perform at a higher level. The sports medicine literature is replete with trials that demonstrate that healthy individuals taking creatine achieve a significant increase in lean body mass in comparison with placebo and may also improve muscle function. [5-17] Increase in muscle mass may be secondary to the athlete's ability to maintain a program of physical activity, although it remains possible that creatine may have a direct effect on muscle protein synthesis.

A creatine trial including normally active older men (59 to 72 years of age) used a double-blind, placebo-controlled design with repeated measures and showed improved muscle performance with seven days of administration trial.[20] These data indicate that seven days of creatine supplementation was effective at increasing several indices of muscle performance, including functional tests in older men without adverse side effects. Creatine supplementation may be a useful therapeutic strategy for older adults to attenuate loss in muscle strength and performance of functional living tasks.

If the sports medicine data on creatine are applicable without intense exercise programs, perhaps creatine may also be used adjunctively to rebuild the muscles of cancer patients. Currently, evidence on this straightforward proposition is not available, as there are few crossover studies from sports medicine to wasting disorders and additional research is clearly needed. Creatine is regarded as a safe supplement for healthy people and is available over the counter in health food stores, as only minor adverse effects have been reported. Mild abnormalities in renal function may occur.[12] Creatine has not been tested in cancer patients, and if considered, should be used with with caution in individuals with renal impairment or with fragile electrolyte balance.

Anabolic Agents. Testosterone was identified and characterized more than 70 years ago and recognized shortly thereafter as a hormone that stimulated muscle growth. Many clinical studies report that testosterone and its analogs support muscle growth,[30-36] yet anabolic steroids have only achieved a tentative hold in medical practice aside from their use in clearly demonstrated hypogonadal states. Physicians have been slow to act on the possible applications of anabolic steroids in patients with catabolic losses of muscle mass. In part, this lack of use stems from the tainted association with illicit use of these compounds, as well as lack of clinical studies until the past decade. In addition, the long-term effects of androgens, which may include virilizing in women, liver damage in both sexes, and adverse changes in serum lipids, have discouraged their use. More recent studies with attenuated androgens, also known as anabolic agents, have limited some of these concerns. In view of the profound suffering associated with wasting and chronic illness, and in view of the very substantial improvements in the efficacy and side-effect profile of these compounds, a re-evaluation of the role of anabolic steroids in these conditions is currently underway.

If the sports medicine data on creatine are applicable without intense exercise programs, perhaps creatine may also be used adjunctively to rebuild the muscles of cancer patients.

Testosterone levels are commonly reduced in patients with severe illness. For example, a hypogonadal state is often present in patients with advanced lung cancer.[31,35] Testosterone replacement is simply accomplished, but the androgen status of cancer patients has been assessed only on a few highly selected patients. Studies on healthy males indicate that supraphysiologic injections of testosterone or its analogs induce muscle synthesis with short-term use. Testosterone replacement in elderly men, men undergoing knee replacement, and AIDS patients is associated with improved muscle size and function. [33,37,38]

A few studies of testosterone or anabolic agents in treatment of weight loss and inanition in patients with cancer have been carried out. A recently reported trial of oxandrolone (an oral synthetic derivative of testosterone) concluded that weight-losing cancer patients on this agent not only gained weight, but their weight gain was also associated with improvement in lean body mass, improved ECOG performance status, and quality of life scores, including the functional component.[34,39,40]

This work is particularly interesting because it also demonstrated that men showed greater gains in lean body mass. Preliminary data demonstrated that when patients were stratified into those who lost weight, stayed weight stable, and gained weight during oxandrolone treatment, the most responsive group of men gained up to 13.9 pounds over a four-month period and the majority of this (10.9 pounds) was lean body mass.[39] This result—net gain of lean body mass—is in striking contrast to the often-expressed belief that cancer cachexia is inevitable and that its progression is unstoppable.

A subsequent placebo-controlled study of oxandrolone confirmed the results of the open label study referenced above, with significant increases in weight and lean tissue weight at month two of a four-month study.[34,40] These studies extend some of the earlier results noted with the injectable anabolic androgenic steroid, nandrolone.[41-43] These data address the potential effectiveness and safety of anabolic agents in cancer-related weight loss. [41-44] While many believe it is not possible to maintain weight in patients with advanced malignancy, others have established that important gains of weight and lean tissue are possible.

In addition, in view of the evidence of hypogonadism in patients with advanced cancer, it may be possible to ask if there is any reason not to offer testosterone replacement to patients with clinical evidence of androgen deficiency, if the patient so desires.

Amino Acids. While anabolic therapy directed at the lean tissues seems unlikely to be entirely successful without provision of the amino acids required for protein anabolism, this area of research is relatively neglected. Only a small number of studies look at amino acid supplementation in cancer patients, and the specific amino acids supplemented are suggested by a relatively sparse literature on amino acid utilization in tumor-bearing animals.

Supplemental oral N-acetyl-cysteine was reported to improve quality of life and increase plasma albumin levels and body cell mass in patients with various forms of inoperable cancer, suggesting that cysteine becomes a conditionally dietary essential amino acid in cancer.[45] The lack of a difference in survival between treated and control groups indirectly suggests that supplemental cysteine did not enhance tumor growth.

An amino acid mixture containing glutamine, arginine, and β-hydroxy β-methyl butyrate (a metabolite of leucine) promoted deposition of lean body mass in non-small cell lung cancer patients without any reported side-effects.[46] This proprietary product originated as a sports supplement and is currently being assessed in a number of larger, ongoing randomized trials. To formulate amino acid mixtures optimized to support anabolism and function in cancer patients, formal assessments of amino acid requirements using current methods are much needed.

CONCLUSION

The few available trials suggest that in cancer patients, resistance training, adequate protein, and amino acid or amino acid derivative supplementation can each individually promote net gain of lean body mass and associated function. If these observations are borne out, it seems possible to conjecture that a combination therapy involving several or all of these may hold the promise of much more important gains—as seen in healthy people. In the age of high technology and super-drugs, this potential solution to cancer-associated wasting may simply be too obvious or not sufficiently glamorous to have merited attention. On the other hand, if it were possible that these effectors were additive or even synergistic in their actions on muscle of cancer patients, then 10 or 20 pounds of tissue gain may be realizable in the context of a multimodality strategy for promoting anabolism in individuals with cachexia.

This approach, which stems from basic muscle physiology, does not necessarily address the question of tumor-derived catabolic factors. Recent work of Tisdale and colleagues suggest that tumors secrete novel lipolysis-inducing factors as well as potent catabolic factors specific for skeletal muscle.[1] The nature and mechanisms of action of these factors are beginning to be elucidated, and these will form the basis of targeted therapies, including aspects that may have an anticatabolic effect.

Vickie E. Baracos, PhD, is professor of protein metabolism in the Department of Nutrition Science and Oncology at the University of Alberta in Alberta, Canada.

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Multimodality Approaches to Optimize Survivorship Outcomes: Body Composition, Exercise, and Nutrition

by Faith D. Ottery, MD, PhD, Suzanne R. Kasenic, RD, and Regina S. Cunningham, PhD, RN, AOCN®

IN BRIEF

Our perceptions of the effects of deterioration in nutritional status and body composition must expand beyond the realm of acute toxicity to one of long-term and quality survivorship. The cornerstone for addressing appropriate body composition and metabolic balance in patients with cancer is a multimodality approach that combines nutrition, physical activity (aerobic and resistance exercises), and pharmacologic intervention as necessary. This integrated approach is important from time of diagnosis through treatment and in long-term survival.

Once, in giving a nutritional presentation to the National Surgical Adjuvant Breast and Bowel Project, I made the comment that the initials NSABP actually referred to the phrase "Nutritional Stability Always Brings Pleasure."

In other words, significant changes—increases or decreases—in a patient's weight or body composition are undesirable for anyone going through cancer treatment. This perspective allows a consistent and integrated philosophic approach to cancer care, whether one is addressing a postmenopausal woman with breast cancer who is at risk for significant weight gain and potential adverse oncologic outcomes or the patients with cancers in which progressive weight loss and cachexia may be the rule, also associated with adverse outcomes.

The cornerstone for addressing appropriate body composition and metabolic balance in patients with cancer is a multimodality approach that combines nutrition, physical activity (aerobic and resistance exercises), and pharmacologic intervention as necessary. This integrated approach is important from time of diagnosis through treatment and in long-term survival.

PHYSICAL ACTIVITY AND SURVIVORSHIP

"Life is a metabolic dance between anabolic and catabolic processes."[1] Optimal cancer rehabilitation techniques should focus both on the reduction of unnecessary catabolic processes (such as unnecessary activity restrictions or anemia) as well as building on anabolic processes to optimize daily functioning and quality of survivorship (QOS).

Family members and clinicians frequently advise people with cancer to rest and to reduce the amount and intensity of their activities—both during and after treatment.[1] Interestingly, these recommendations may exacerbate the fatigue that plagues the survivor. In fact, living alone may actually contribute to improved functionality as well as supporting continued independence. Physical inactivity can contribute to disuse muscle atrophy, contributing to loss of cardiorespiratory fitness and to fatigue. Catabolic losses of weight that occur as the result of cytokine-mediated changes in metabolism or chronic use of corticosteroids can also contribute significantly to loss of muscle mass during cancer treatment. The combined losses of weight and lean tissue may be synergistic and if not reversed with cancer rehabilitation may progress further over time due to impaired physical activity.

Structure and function of muscle and bone are dependent on physical activity combined with appropriate nutrition and hormonal milieu supporting anabolism. In healthy volunteers, complete bed rest for as short as a week has been associated with a 1-4 percent loss of muscle mass and a number of metabolic changes including insulin resistance and increase in extremity fat.[2-4] These changes can be exacerbated in the setting of fever, corticosteroids, and the proinflammatory cytokines associated with malignancy. Each of these settings is also associated with mobilization of bone calcium, again with implications for the long-term survivor.

Accelerated loss of bone mineral density, with its ensuing complications of pain and risk for compression and other pathological or traumatic fractures, becomes increasingly important with increased survivorship—in terms of both numbers of survivors and duration of survivorship. Inactivity, combined with direct complications of chemotherapy and changes in the survivor's hormonal milieu (orchiectomy, contraindications to hormone replacement therapy or HRT, and corticosteroid use) all contribute to increased risk of progressive bone demineralization and osteoporosis. Resistance exercise is increasingly recognized as an important therapeutic intervention for preventing or reversing bone loss and its complications.[5-11]

Studies of physical exercise in cancer initially focused on aerobic exercise in women with breast cancer.[12] More recently, resistance exercise has been added to the regimens with impact on cardiorespiratory fitness, improved body composition with increased lean tissue and decrease in fat mass, as well as improved strength and functionality. There is an increasing body of literature supporting the importance of physical exercise in cancer survivors with a variety of different cancer types with demonstrated improvement in 1) functional capacity, 2) perception and measured

fatigue, 3) lessening requirements for medications for nausea or pain, 4) psychological or emotional aspects of improved self-esteem, mood, sense of control, overall sense of well-being, reduced depression and anxiety, and 5) immunologic function as assessed by increased natural killer cell activity.[13-19]

The specific physical aspects of cancer rehabilitation can include one or more of the following: deficit-related physical and occupational therapy; individual or group exercise programs; institutional, gym, home-based, or nature-based programs; aerobic (walking, cycling, swimming, dancing), stretching, and resistance exercise (elasticized resistance bands, light-to-moderate weight lifting).

CORTICOSTEROIDS: CHRONIC MUSCULOSKELETAL SEQUELAE

Corticosteroids have a number of physiologic effects that contribute to broad use in patients receiving cancer therapy as well as in treatment of survivor co-morbidities. Antiemetic, anti-inflammatory, and antineoplastic roles are common as well as used in terminal palliative care for its central effects to improve sense of well-being and short-term improvements in affect and appetite.

In the context of the current discussion, it is important to consider the effects of glucocorticosteroids on lean tissue and the skeleton. The development of muscle weakness and atrophy is a well-known complication of therapy with exogenous glucocorticosteroids, and is probably the most common form of drug-induced myopathy encountered in clinical practice.[20-22] The clinical presentation of steroid-induced muscle weakness is characterized by an insidious onset and is usually painless. The proximal muscles of the arms and legs are affected first with the lower extremities demonstrating the earliest signs of weakness. There is a relative sparing of distal musculature, and smooth muscle does not appear to be involved. The patient first notes difficulty climbing stairs and rising from low chairs because hip girdle and thigh weakness, but by the time this occurs marked muscle atrophy is evident. In addition to effects on muscle, glucocorticoids also contribute significantly to bone demineralization and risk for progressive osteoporosis.

In review of the published literature, exercise is increasingly included as integral to any intervention addressing prevention or treatment of musculoskeletal complications of corticosteroids, regardless of the underlying disease state utilizing chronic corticosteroids.

Prevention and treatment of corticosteroid-induced osteoporosis is based upon general measures such as calcium and vitamin D supplementation, adequate protein intake, regular physical exercise, hormonal replacement therapy and upon specific means like therapies used in primary osteoporosis. Bisphosphonates, which are potent bone resorption inhibitors, have been shown to increase bone mineral density and to decrease fracture rate.

SYNERGY OF NUTRITION AND EXERCISE IN SURVIVORSHIP

Support of whole-body anabolism is based on an integrated approach of nutrition, exercise, and support of an appropriate hormonal milieu. Probably the most important aspects of a synergistic multimodality approach are 1) awareness, 2) assessment, and 3) appropriate intervention.

Lack of awareness regarding the impact of nutrition and body compositional changes on acute and chronic aspects of survivorship as well as a lack of awareness of cost-effective interventional options are the two greatest impediments to success in addressing acute and chronic sequelae of cancer therapy. Table 1 addresses the specifics of this approach. Components as simple as the intake of adequate protein in chemotherapy toxicity and loss of muscle mass and function in individuals on bed rest to the chronic sequelae of malnutrition and body compositional change have long been underappreciated in the armamentarium of the oncologist and are now beginning to play a role as we address issues of survivorship.

Since the inception of the Association of Community Cancer Centers (ACCC) 30 years ago, the Association has set standards of integrated quality oncology care. Evolution of standardized assessment, as well as recent research in multimodality intervention, offer new insight that is immediately applicable to the oncology team. Today the role of exercise, specialty nutriceutricals containing omega-3 fatty acids[23] (ProSure®, Resource Support®) or β-hydroxy β-methylbutyrate (HMB) with glutamine and arginine[24] (Juven®), anticatabolic agents such thalidomide[25] (Thalomide®), and now anabolic agents such as oxandrolone [26-28] (Oxandrin®) demonstrate increases in total weight or slowing of weight loss, increase in lean tissue weight, all of which are with associated functional and quality of life improvements. A newly launched NCI-sponsored study addressing an integrated approach of nutrition, exercise and pharmacologic intervention (oxandrolone vs. megestrol acetate) characterizes the new model of multimodality approaches for improving quality of cancer survivorship.

Faith D. Ottery, MD, PhD, is current chair of the Rehabilitation Committee of the Multinational Association of Supportive Care in Cancer and director of medical affairs in oncology, HIV, and geriatrics for Savient Pharmaceuticals, Inc. Suzanne R. Kasenic, RD, is oncology nutritionist at Fox Chase Temple Cancer Center in Philadelphia, Pa. Regina S. Cunningham, PhD, RN, AOCN® is chief nursing officer and director of Ambulatory Services at the Cancer Institute of New Jersey in New Brunswick, N.J.

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Table 1. Practical Assessments in Prevention and Treatment of Chronic Sequelae of Cancer Therapy

Variable	Assessment	Intervention
Nutritional Status		
Weight, weight history	Scale, PG-SGA*	
Nutritional intake	Patient history, PG-SGA, protein/calorie counts	Nutritional intervention ■ Define macronutrient goals Protein 0.7 g/lb of ideal weight (1.5 g/kg)/day Calories 16-18^{+} kcal/lb current weight ■ Micronutrient—multivitamin and vitamin, mineral as indicated ■ Consideration of commercial nutritional supplements ■ Consideration of specialty nutriceuticals: HMB or omega-3 Pharmacologic intervention ■ Antiemetics, analgesics, antidepressants; orexigenic, anticatabolic/antimetabolic or anabolic agents; others
Nutrition impact symptoms	Patient history, PG-SGA	Behavioral intervention ■ Address taste and smell sensory changes ■ CAM: ginger, ice, behavioral Pharmacologic intervention ■ Antiemetics, analgesics, antidepressants; orexigenic, anticatabolic/antimetabolic or anabolic agents; others
Catabolic/metabolic stresses	Vitals, concommitant meds, PG-SGA	Pharmacologic intervention ■ Anticatabolic/antimetabolic or anabolic agents, others
Physical examination: muscle, fat, fluid	Focused physical exam, PG-SGA	Behavioral intervention ■ Mixed modality exercise (aerobic, resistance/strength) Pharmacological intervention ■ Orexigenic, anticatabolic/antimetabolic or anabolic agents; diuretics
Body Composition/Bone Mineral Density		Behavioral intervention ■ Mixed modality exercise (aerobic, resistance/strength) Pharmacological intervention ■ Orexigenic, anticatabolic/antimetabolic or anabolic agents; diuretics; vitamins A and D, calcium, magnesium; bisphosphonates, parathyroid hormone, other
Physical examination: muscle, fat, fluid	PG-SGA, anthropometrics	
Body composition assessment	Bioelectrical impedance analysis (BIA) Dual energy X-ray absorptiometry (DEXA)	
Functionality		Behavioral intervention ■ Mixed modality exercise (aerobic, strength-resistance bands, weight lifting)

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Variable	Assessment	Intervention
Functionality *continued*		Pharmacological intervention ■ Antiemetics, analgesics, antidepressants; or exigenic, anticatabolic/antimetabolic or anabolic agents; diuretics; vitamins A and D, calcium, magnesium, bisphosphonates, parathyroid hormone, other
Assessment of activities of daily living	ECOG/Zubrod, Karnofsky, PG-SGA	
Assessment of change from individual's norm	How fast? How often? How long to recover?	
	Borg scale of perceived exertion	
Endurance	6-minute walk	
Strength	Rise from chair, other, handgrip strength	

*The Patient-Generated Subjective Global Assessment (PG-SGA) tool and worksheets are for patient or clinician use. They can be found on ACCC's web site at *www.accc-cancer.org/publications/pgsga.pdf*, and *www.accc-cancer.org/publications/pgsgaworksheet.pdf*. The PG-SGA addresses the global status of the patient from this integrated perspective—weight loss and weight loss history, nutritional intake, nutrition impact symptoms, ECOG performance status in patient terms, metabolic/catabolic stresses, and physical examination focused on body composition. From the standpoint of functionality, ECOG or Karnofsky performance status assessments are important prognostic indicators, but greater insight may be obtained in terms of functionality and QOS with questions addressing change in functioning as it impacts that survivor.

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