SPECIAL ISSUE

Oncology

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SARA THYR, ND, graduated from Bastyr University’s naturopathic medicine and midwifery programs. She was president of the New Hampshire Association of Naturopathic Physicians and was appointed by then-Governor Lynch to the New Hampshire Board of Naturopathic Examiners. She has served 2 terms on the board of directors for the American Association of Naturopathic Physicians. Thyr is a popular public lecturer, providing continuing education lectures to naturopathic physicians as well as medical doctors, midwives, and nurse practitioners. In 2008 Thyr moved to Petaluma, California, where she founded Willowbend Natural Medicine.

HEATHER WRIGHT, ND, FABNO, has worked at Cancer Treatment Centers of America in Philadelphia for 7 years. She earned her undergraduate degree in 1995 at St Lawrence University, New York, completed an internship in community medicine in east Africa, and worked in the Harvard Mallinckrodt Laboratory of Molecular and Cellular Biochemistry, Cambridge, Massachusetts. She earned her doctorate of naturopathic medicine from Bastyr University in 2005. Wright is currently vice president of the Oncology Association of Naturopathic Physicians.
MESSAGE FROM THE PUBLISHER

The Face of Integrative Cancer Care

Cancer affects all age groups and does not discriminate against men, women, or children. Nearly all practitioners—even those not involved directly with oncology—have seen a person who has or has had cancer in their practice. That’s because many cancer patients and survivors are interested in an integrative approach to health that will help them not only survive, but thrive.

The contributors to this special oncology issue of *Natural Medicine Journal* fully understand and are devoted to the men, women, and children touched by this disease each year.

I would like to extend a special thank you to our guest editor, Heather Wright, ND, FABNO. In addition to being integral to the planning of this issue, Wright also updates us on the latest research on IV vitamin C in patients with advanced cancer in her Abstract & Commentary on page 20. Keri Marshall, ND, comments on a study involving essential fatty acids and breast cancer survivors in her article on page 26. The peer-reviewed paper (page 6) tackles the commonly diagnosed and difficult-to-treat issue of cancer cachexia. This issue also features commentary on mushrooms and prostate cancer (page 28), honey and hot flashes (page 30), the benefits of exercise during cancer treatment (page 32), and more.

We hope you enjoy this special issue and share it with your colleagues. Both oncology and non-oncology integrative practitioners should keep up on integrative cancer care, because the face of cancer is everywhere.

In good health,

Karolyn A. Gazella  
Publisher, *Natural Medicine Journal*
Navigating the Complex Terrain of Cancer Cachexia

By Rebecca Snowden, ND, LAc

ABSTRACT
Cancer cachexia is a multifactorial syndrome characterized by loss of lean body mass, which may adversely affect a patient’s overall survival, quality of life, level of physical activity, and ability to receive antineoplastic therapy.1 Where full eradication of tumor burden is not achieved, multimodal prevention or treatment of cachexia is indicated. This article serves to highlight strategies to consider based on available evidence and treatment goals in cancer cachexia.

INTRODUCTION
Cachexia is a condition secondary to a primary disease process characterized by wasting, weight loss, muscle atrophy, fatigue, weakness, and loss of appetite in patients not actively trying to lose weight or making behavioral or lifestyle changes. It is estimated to be the cause of death in more than 30% of cancer patients, and more than half of all cancer patients have cachexia at the time of death.22 In advanced cancer, the prevalence of cachexia is thought to be between 60% and 80%.22

Precise percentages of cachexia prevalence are, however, difficult to capture due to the use of different criteria to define cachexia by the various reporting groups. Regardless, there is an urgent need to employ supportive care strategies that may effectively work to prevent or slow the development of cachexia and thereby improve treatment tolerance, response to treatment, quality of life, and overall survival.33

CLASSIFICATION OF CACHESIA STAGES
A diagnostic framework developed in 2011 has been proposed that defines cancer cachexia as occurring along a continuum consisting of 3 stages: precachexia, cachexia, and refractory cachexia (Figure 1).4 The precachexia stage is classified as including anorexia, metabolic changes, and weight loss ≤5% in the previous 6 months.4 The cachexia stage is classified as involving weight loss >5% (or weight loss >2% if the patient has BMI<20 or sarcopenia) and often with decreased food intake and systemic inflammation.4 The refractory cachexia stage is classified as involving low performance status (ECOG score 3 or 4), prognosis of <3 months, and malignant disease that is both procatabolic and unresponsive to antineoplastic therapy.4 Proposed refinements have been made to the criteria of the precachexia stage, yet challenges persist in defining its parameters in a way that makes it a clinically relevant tool.5 The concept of precachexia, however, is important to grasp in that this is the stage at which metabolic changes have already begun to take place and progression to cachexia may be prevented by initiation of early interventions. This initial period of the cancer cachexia trajectory tends to be barely perceptible clinically and thus can be easily missed. Reversible risk factors should be addressed as early as possible on the continuum and must continue to be addressed through the cachexia stages. Identification of refractory cachexia is useful in determining when ethical considerations should be evaluated in the goals of naturopathic supportive care, and a shift to strictly palliative support should be discussed at that time.

Figure 1. The stages of cancer cachexia.

RISK FACTORS, PATHOPHYSIOLOGY, AND DIAGNOSTICS
There are several risk factors for cancer cachexia, most of which are reversible if caught early enough (Figure 2). Risk factors include constipation, depression, inflammation, insulin resistance, male hypogonadism, low self-esteem, decreased appetite, and decreased food intake.1 In cancer patients, decreased appetite may be due to standard antineoplastic treatment–related toxicities such as dysgeusia, nausea and vomiting, odynophagia from mucositis, and early satiety after major

(continued on page 8)
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abdominal surgical procedures. Psychosocial factors such as depression or increased stress also may contribute to decreased appetite. Cancer-related metabolic changes are considered a primary driving force behind decreases in appetite not due to treatment or psychosocial-related factors, which, along with loss of lean body mass, characterize the catabolic process associated with cachexia.1

Cancer-related metabolic changes include increases in muscle catabolism, resting energy expenditure, metabolism, cortisol, inflammatory cytokine production, and insulin resistance. While the governing process to these systemic catabolic changes remains unknown, recent evidence implicates a central nervous system role—namely chronic hypothalamic inflammation—as a possible source.6

Cachexia is characterized by lean muscle loss as the body shifts from an anabolic state to a catabolic state, progressive fatigue and weakness, and a decline in performance status. As fatigue and anorexia may manifest in cancer patients for various reasons, it is weight loss with decreased muscle strength that can help identify cachexia.1 Dynamometry or muscle strength testing may be employed for this assessment. However, more often, gross evaluation of strength is assessed through resistive force testing of the arms and upper legs by a clinician.

Diagnostic lab markers may be used to identify the magnitude of cancer-related metabolic changes. These might include but are not limited to C-reactive protein (CRP), serum albumin, hemoglobin, TNF-alpha, IL-6, ghrelin and leptin.1,7-10 Although no formal validated guidelines currently exist on specific parameters to diagnose cachexia, in 2008 it was proposed that any elevation seen in CRP or IL-6 or any decrease in hemoglobin or serum albumin might be used in combination with other parameters such as anorexia, fatigue, decreased muscle strength, and loss of lean body mass to arrive at a diagnosis of cachexia.9 A study of 136 male cancer patients in 2012 found that elevation of TNF-alpha and IL-6 independently predicted survival beyond cancer stage alone; however, the researchers found that low serum albumin alongside weight loss made use of parameters that were more readily available and that offered similar ability in predicting survival as compared to inflammatory markers.7 A 2014 study evaluated the utility of ghrelin and leptin in diagnosing cachexia and predicting survival. Researchers found that ghrelin levels above 663 ng/mL (sensitivity 83%; specificity 98%) and leptin levels below 31 ng/mL (sensitivity 79%; specificity 73%) were superior to the use of low albumin (sensitivity 63%; specificity 69.4%) in diagnosing cachexia and predicting survival.11 While laboratory biomarkers may be promising in the context of identifying the presence or magnitude of cachexia, values also may be abnormal due to other factors and cachexia can sometimes be present without abnormalities in these markers. Their use therefore may have limited clinical value.

A 2015 comprehensive review of 27 clinical trials on bioelectrical impedance analysis (BIA)/phase angle found that BIA/phase angle measurements “can benefit in the clinical management of cancer patients in multiple ways: in the prevention; diagnosis; prognosis; and outcomes related to treatments that affect nutritional and overall health status.”10 BIA measures resistance and reactance of electric current in body tissues. From these values, measures of total body water, fat-free mass, and fat mass can be derived. Phase angle is a measure derived directly from the resistance and reactance values and serves as an independent prognostic variable. A low phase angle correlates with increased malnutrition status, increased severity (continued on page 10)
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of disease, and lower overall survival. BIA measurements are of greatest utility when obtained at baseline and repeated throughout an individual’s course of treatment, measuring changes in an individual over time. In this way, the efficacy of management and predictive value of the longitudinal changes can be better determined so that supportive care strategies can be modified accordingly and aggressiveness of nutritional interventions increased or decreased as needed.10

TREATMENT OF CACHEXIA

There is no better way to treat and reverse cachexia than to decrease the overall tumor burden, but in cases in which full eradication of tumor burden is not achieved, multimodal prevention or treatment of cachexia is indicated. Conventional methods beyond treating the cancer itself include pharmaceutical agents such as appetite stimulants (eg, megestrol acetate, dronabinol), steroids, testosterone, or nonsteroidal anti-inflammatory drugs. Studies have shown that a combination of integrative therapies has significantly improved outcomes in the treatment of cancer cachexia vs use of a single therapy alone.12-16 There is a consensus among experts that multimodal treatment (medication, nutrition, and other non-pharmaceutical strategies) to address the various contributing factors to cachexia should be offered to cancer patients in the precachexia and cachexia stages.17,18

Nutritional counseling in cachexia typically focuses on increasing protein and caloric intake. Based on this nutritional approach as a single modality, evidence strongly suggests that early intervention in precachexia prior to CRP elevation can be effective in preventing or slowing weight loss.1,4,18 Evidence to suggest there is benefit of increased protein and caloric intake on physical function or quality of life once in the refractory cachexia stage is insufficient; however, nutritional counseling in this stage may be beneficial in helping the patient and caregivers understand the changes occurring and the limitations of nutrition during this time.18 Ultimately, once the systemic inflammatory response has begun, increased protein and caloric intake alone are inadequate to maintain weight as the inflammatory response dampens anabolism.1 In consideration of the implications of systemic inflammation along the cachexia continuum and the inability of increased protein and caloric intake alone to address the catabolic process, it is advised to continue encouraging anti-inflammatory food choices that also reduce oxidative stress and insulin resistance while providing essential nutrients even in the palliative care setting.19 A thoughtful approach should be taken in encouraging food choices that will both meet the protein and caloric intake goals and prevent worsening of other host conditions that contribute to cachexia progression. Although dietary approaches such as ketogenic diets and fasting are sometimes recommended for cancer patients, human clinical trial data on the effects of these specific strategies on the progression of cachexia in precachectic or cachectic cancer patients are not available at the time of this writing. However, consistent restriction (vs intermittent restriction) of calories or protein is suspected to worsen cachexia and is thus not advised for this patient population.

Exercise may attenuate the catabolic process of cachexia through several mechanisms, including decreasing insulin resistance, reducing inflammation, and modulating the breakdown of muscle mass.20 Though clinical trials of exercise therapy in defined cachectic cancer patient populations are lacking, a Cochrane review concluded there is strong rationale for the use of exercise in cancer cachexia.21 Multiple reviews and opinion articles have been published in support of exercise therapy as early intervention or prevention, as well as throughout more pronounced cachectic states.20,22-27 Both aerobic and resistance training have been shown to be beneficial in preclinical studies, although through different mechanisms. Aerobic activity lends more to attenuation of insulin resistance and inflammation, whereas resistance training exerts positive effects on lean muscle mass and strength.22-25 Arguments could be made for the encouragement of either form, or a combination of the 2, in the cachexia setting. Any specific recommendations should be made with consideration for the individual’s physical limitations, bone health and fracture risk, comorbidities, and preferences. Exercise tolerance may be decreased in patients with significant fatigue, anemia, or cardiac dysfunction. Care should be taken in tailoring exercise recommendations for these patients so as not to exacerbate these conditions.23

(continued on page 12)
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Non-pharmaceutical agents can be used in a multimodal approach that aims at preventing or treating cachexia. Often times, multipurpose supplemental agents such as those discussed in the following paragraphs will also prove useful for improving response to and tolerance of cancer treatments and can be continued throughout the long-term course of care. Use of nutritional, botanical, or vitamin supplements should include consideration of any potential interactions with antineoplastic therapies or medications, and use should be considered on an individual patient basis. Disease-specific and treatment-specific options should be considered in choosing targeted supplement support. For example, use of pancreatic enzymes may be a consideration in the setting of exocrine pancreatic insufficiency secondary to a pancreatic tumor or following resection of the involved malignant tissues. A standard naturopathic approach should also be taken in addressing an individual’s set of risk factors. The following is a look at some agents that may have a role in addressing some of the metabolic changes occurring in cachexia:

- **Amine** supplementation may decrease proteolysis and increase protein synthesis in skeletal muscle. Creatine is an amine thought to improve skeletal muscle mass and function. It was administered in a double-blind, randomized, controlled trial that evaluated its effects on nutritional status, quality of life, and muscle function in 16 colorectal cancer patients. Participants took 5 g twice daily for the first week, followed by 2.5 g twice daily for 7 weeks. Results showed a significant improvement in phase angle after 8 weeks of creatine supplementation.

- **L-carnitine** deficiency is thought to contribute to cancer cachexia progression. L-carnitine has been used in 2 randomized phase III clinical trials evaluating multimodal treatment in cancer cachexia, both of which showed improved outcomes in the combination-therapy arms.

- **Omega-3 fatty acid** supplementation has been widely reviewed for extensive clinical trial evidence supporting its utility in improving clinical outcomes in cancer. Reviews consistently suggest that increased quality of life, increased physical activity, improved response to chemotherapy, and decreased inflammation are among the benefits of omega-3 fatty acid supplementation in cancer patients. In the latest review, authors concluded that omega-3 fatty acids, when used as part of a multimodal strategy, are effective in cachexia. In a randomized, controlled, crossover trial of 20 healthy subjects to evaluate the effects on appetite of 3 g EPA+DHA taken daily for 3 weeks, results were significant for less postprandial sensation of fullness in both genders and, in women, a significant increase in desire to eat with use of fish oil supplementation. A randomized controlled trial (N=68) comparing the daily use of a standard protein-and energy-dense nutritional formula to a comparable one enriched with omega-3 fatty acids (7.24 g daily), probiotics, and additional micronutrients showed a statistically significant (P<0.05) increase in body weight in cachectic head and neck cancer patients undergoing an 8-week course of radiation treatment when the omega-3 fatty acid–enriched formula was used during and 1 month after their radiation course vs the standard formula. A single-arm phase II study evaluating the use of combination therapy taken daily for 4 months consisting of antioxidants, a nutritional formula enriched with omega-3 fatty acids (3.12 EPA+DHA per day), medroxyprogesterone acetate, and celecoxib showed significant improvement in body weight, lean body mass and appetite in the 39 patients with advanced cancer.
who presented at baseline with cancer-related anorexia/cachexia. In a phase III randomized study, 332 patients with cancer-related anorexia/cachexia were assigned to 1 of 5 treatment arms: arm 1, medroxyprogesterone or megestrol acetate; arm 2, oral EPA-enriched nutritional formula (2.2 g of EPA daily); arm 3, L-carnitine; arm 4, thalidomide; arm 5, a combination of therapies used in arms 1-4. Treatment was of 4 months' duration, and results showed superiority of arm 5 over the other treatment arms, with a significant increase in lean body mass, decrease in resting energy expenditure, improvement in fatigue, increase in appetite, decrease in IL-6 and TNF-alpha, and improvement in performance status.

- **Melatonin** has been shown in clinical trials to be beneficial for cancer patients receiving chemotherapy, radiation, supportive care, or palliative care and to possibly increase overall survival when used as part of a multimodal strategy. The research suggests melatonin has antioxidant, anti-proliferative, and immune-modulating effects and also decreases the intensity of chemotherapy-induced side effects. In regards to cachexia specifically, results of a small clinical trial evaluating melatonin in combination with fish oil showed that the combination had a weight-stabilizing effect in cachectic patients. Results of another clinical trial evaluating melatonin in combination with supportive care vs supportive care alone in patients with metastatic solid tumor showed decreased rate of weight loss in the combination arm. A randomized, double-blind, placebo-controlled study evaluating melatonin as a single therapy for cachexia was conducted in patients with advanced cancer but terminated after only 28 days due to lack of significant differences seen between treatment arms in weight, appetite, and quality of life parameters. However, the authors note that 32% of their patients did not complete the trial due to advanced disease and further suggest that melatonin may have had a more significant role if not initiated so late in the disease trajectory.

- **Other supplements** that may be worth consideration as part of a multimodal approach in the prevention or treatment of cachexia include vitamin D, magnesium, antioxidant therapies, and anti-inflammatory agents such as curcumin, quercetin, and boswellia. These may further address some of the underlying metabolic changes in cancer cachexia; however, they have been less researched for this specific purpose in cachectic patient populations.

**CONCLUSION**

Navigating the complex terrain of cancer cachexia can be done strategically and may improve treatment tolerance, response to treatment, quality of life, and overall survival. As always, physicians must take into consideration all factors relating to the individual patient including but not limited to diagnosis, prognosis, involved sites of disease, symptoms, physical limitations, treatment and related side effects, psychosocial circumstances, socioeconomic factors, cultural and religious backgrounds, and patient preferences. Identifying early on a patient's risk factors for cachexia and addressing them then may slow or reverse the progression of refractory cachexia. Taking action on nutritional, exercise, or supplement recommendations should always be patient-driven, and caregivers should be educated accordingly. Understanding and communicating the limitations of naturopathic support therapies when they are initiated late in the course of the cachexia trajectory can reduce unrealistic expectations and decrease burdens on patients and caregivers while educating them on the changes that are occurring. While ongoing and future clinical trials on multimodal treatments for cancer cachexia are much needed and may help us to achieve improvements in outcomes such as quality of life and overall survival for our patients, the synthesis of currently available evidence this article provides serves as a basis and call for routinely employing an integrated approach in an effort to diminish the suffering experienced by those who are at risk for or affected by cancer cachexia.

**REFERENCES**


The medical community encourages everyone to eat a diet high in oily fish, a major source of the omega-3 fatty acids EPA and DHA. If you’re not eating at least two meals of oily fish per week, a supplement may be the right option for you. Our high-quality, award-winning fish oils, offered in both liquid and soft gel forms, are sourced from fish found in deep, unpolluted cold water. To ensure freshness, potency, and purity, all of our fish oils are third-party tested by an FDA-registered U.S. laboratory.
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Pharmacist Ross Pelton Describes the Role of Probiotics in Oncology
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In this podcast, probiotics expert Ross Pelton, RPh, CCN, discusses the use of probiotics to reduce risk of cancer and as an adjuvant treatment. He also tackles tough topics like the number of strains and dosage.

ABOUT THE EXPERT
Ross Pelton, RPh, CCN, is Essential Formula’s director of science, in addition to being a practicing pharmacist, clinical nutritionist, and health educator in Southern Oregon. Pelton earned his bachelor of science in pharmacy from the University of Wisconsin and received his PhD in psychology and Holistic Health from the University for Humanistic Studies in San Diego, California. A certified clinical nutritionist, Pelton was named as one of the Top 50 Most Influential Pharmacists in the United States by American Druggist magazine for his work in natural medicine. Pelton teaches continuing education programs for healthcare professionals to use natural medicine and integrate it into their practices. He also has authored numerous books, including The Drug-Induced Nutrient Depletion Handbook, which is a gold-standard reference book for health practitioners.

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Cancer and Homeopathy

Cancer and Homeopathy (Narayana Verlag, 2014) by the French oncologist Jean-Lionel Bagot, MD, belongs on the desk of anyone seeing cancer patients regularly. It is designed as a quick clinical reference guide for using homeopathy in supportive care of conventional cancer treatment. It is clear from reading through this handy book that Cancer and Homeopathy is based on Bagot’s years of experience as an oncologist and homeopath. He sees 4,000 patients annually through a supportive oncology care clinic at a hospital, a radiation oncology clinic, and a palliative care unit. His sections are well-designed with guides for troubleshooting, and he provides charts with typical dosing for common side effects encountered with conventional treatments.

In the second part of the book, Bagot describes hetero-isopathy, which is the use of homeopathic remedies made out of the chemotherapy agents themselves (eg, Cyclophosphamide 6C). He also includes remedies for the newest chemotherapeutics: small molecules and immunotherapies. For example, for bullous rash from sorafenib or sunitinib, he recommends Cantharis 6C TID. Short case illustrations are sprinkled throughout the book and make it more engaging.

While I continue to practice constitutional homeopathy, there is a strong argument for combination low-dose remedies in supportive cancer care. Using low-potency, frequent dosing schedules matches the depleted states of many cancer patients. In addition, side effects of treatment tend to be driven less by constitution and more by the medication being used. Bagot provides useful sample regimens that can easily be converted into a liquid combination for patients to add to a water bottle. For instance, an easy combination for peripheral neuropathy would include Nervous medianus 7x, Ars album 12c, Zincum metallicum 6c or 12c, Hypericum 30C, Selenium 6c, Chromium 3c, Calc carb 6c, and Thallium sulphuricum 6c. Or for bone marrow support, one could combine Bagot’s recommendations (Medulla ossium 6X, China 12C, Ferrum mur 3C, Nat mur 6c, Silicea 6C, Crotalus horridus 6C, Phos 6C, and Thymuline 9C) with 3 additional remedies (Carcinosinum 30C, Thuja 12C, and Ruta 12C) based on some recent animal research showing that dosing these remedies for 10 days increased total white blood count, bone marrow cellularity, and enhanced proliferation of B and T lymphoid cells compared to controls. Making low-dose combinations in liquid forms for patients makes it easier for patients to be compliant with dosing and simplifies treatment during an already overwhelming time.

On the other hand, it is quite difficult to find the hetero-isopathy remedies (eg, Cisplatinum 7CH). Most of the obscure, generic remedies for cancer side effects like Picric acidum and Thallium sulphuricum are available from Hahnemann labs in California, Helios in the United Kingdom, or Remedia in Austria. Finding the chemotherapy remedies, however, may take a lot of detective work. Also, be clear with your patients and their caregivers that these are homeopathic versions of the medications, not the controlled substances themselves.

One other downside to Bagot’s book is that, while it is very comprehensive in addressing adjunctive cancer care, it fails to reference the homeopathic doctors and source materials that make up the homeopathic content of the book. Today we are fortunate to be building upon a long and rich scientific history in homeopathy. As Isaac Newton wrote, “If I have seen further, it is by standing on the shoulders of giants.”

May the book Cancer and Homeopathy help you see further—and discover more options for helping your cancer patients.

Excerpts of the book, including the section on neuropathy, are available here.

REFERENCES
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High-Dose Intravenous Vitamin C in Cancer Care

Phase I-II clinical trial looks at intravenous vitamin C combined with chemo

By Heather Wright, ND, FABNO

REFERENCE

STUDY OBJECTIVES
The study aimed to
1. determine the safety and tolerability of 1.5 g/kg intravenous vitamin C (IVC) over 90-120 minutes given 2-3 times per week to cancer patients during the course of chemotherapy including documentation of side effects and toxicity;
2. determine pharmacokinetics by measuring plasma vitamin C and urinary oxalic acid before, during, and after treatment with IVC and chemotherapy;
3. identify any cancer types and treatments that might be favorable to combine with IVC if possible; and
4. measure quality of life (QoL) and mood monthly throughout the study.

DESIGN
Single dose Phase IIA pilot study

PARTICIPANTS
Oncology patients ages 47 to 76 were referred from within a medical university–affiliated cancer center and were eligible if they had an Eastern Co-operative Oncology Group (ECOG) status 0-1, a CT and staging workup within the 4 weeks of the first IVC treatment on protocol, normal red blood cell glucose 6 phosphate dehydrogenase (G6PD) activity, serum creatinine ≤175 μmol/L, and the judgment of their treating oncologist that standard of care or off-label cytotoxic chemotherapy offered less than a 33% likelihood of an objective clinical response. The study evaluated 31 people, enrolled 16, analyzed 12, and described 14 (7 males, 7 females).

STUDY PARAMETERS ASSESSED
CT scan of chest, abdomen, and pelvis performed 4 weeks before treatment and approximately every second chemotherapy cycle with assessment for any response using Response Evaluation Criteria in Solid Tumors (RECIST 1.0).

The following were measured at study entry and every 4 weeks:
• tumor markers,
• complete blood count (CBC),
• metabolic panel,
• C-reactive protein (CRP),
• physical exam, and
• coagulation profile.

The following were measured at baseline, at 2 weeks, and then monthly:
• Functional Assessment of Cancer Therapy-General (FACT-G) quality of life questionnaire scores; range from 1 to 108
• Profile Mood States-B questionnaire giving Total Mood disturbance score; range from -20 to 100

Less than 7 days prior to first chemotherapy dose, plasma vitamin C levels and urinary oxalic acid were measured during and after the administration of 0.6 g/kg IVC given over 90 minutes. The same was performed again 3 days after chemotherapy administration.

Adverse events were evaluated using National Cancer Institute clinical criteria 3.0.

PRIMARY OUTCOME MEASURES
Safety and tolerability of 1.5 g/kg IVC given concurrent to chemotherapy regimens (although not given on the same day) in a heterogeneous advanced disease cancer population via descriptive analysis using quality of life and mood questionnaires and individual case synopsis.

Pre- and post-chemotherapy pharmacokinetics of IVC in humans with advanced cancer via measurement of plasma IVC and urinary oxalate levels before, during, and after treatment.

KEY FINDINGS
IVC was nontoxic for all participants. Side effects of thirst and increased urinary flow were common symptoms during all IVC infusions. Other side effects included nausea and vomiting, unpleasant fluttering sensation, chills, headaches, and a rumbling feeling in the abdomen. One patient experienced increased lower extremity edema. One patient reported a mentally hazy feeling on the day after infusion.

Mean baseline plasma vitamin C concentrations changed from 66.4±74.9 μmol/L before IVC and chemotherapy was initiated to 131.6±102.0 μmol/L after treatment (P<0.031). Total urinary excretion profiles before chemotherapy was initiated (149±49.3) were higher than after (133±40.0), suggesting a short-term tissue retention of vitamin C after chemotherapy (P<0.099) with no significant increase in total urinary oxalic acid excretion (P<0.850).

Three patients with different types of cancer experienced unexpected transient stable disease, increased energy, and functional improvement.
PRACTICE IMPLICATIONS

Pilot studies should provide a clear list of aims and objectives within a formal framework to encourage methodological rigor, produce a work that is scientifically valid and publishable, and lead to higher-quality RCTs. ¹

For our purposes as integrative providers, we hope that an IVC pilot will help us focus efforts and find key reasons larger studies should move forward. In vitro and preclinical data report IVC to have pro-oxidative and antitumor effects.²⁻⁴ Human clinical trials have not found clear-cut antitumor response but have achieved high blood millimolar concentrations of ascorbate in humans (10+ mmol/L) similar to in vitro (5 mmol/L) and preclinical models (10 mmol/L) that have demonstrated antitumor effects. At this point human IVC clinical trials collectively suggest that improved quality of life and reduction in symptoms of disease and/or side effects of cancer treatment may be attributed to treatment with IVC.⁵⁻⁹

Although this pilot study is based on a non–statistically representative population, and therefore is limited in practice implications, it does raise some points to consider.

This study is one of a growing body of studies finding safety and tolerability of IVC in patients with advanced disease receiving standard chemotherapy regimens.⁹⁻¹⁴ The study describes 14 cases of people with different tumor types (6 colorectal, 2 lung, 1 cervical, 1 breast, 1 ovarian, 1 bladder, 1 tonsil, 1 biliary) who receive IVC 2-3 times weekly during treatment with chemotherapy regimens where the oncologist determines there’s less than 33% chance the chemo may have efficacy.

The first author of this study published another important Phase I pilot study in 2008 that reported IVC is safe and well-tolerated in humans with advanced malignancy and established a safe and tolerated dose of 1.5 g/kg given 3 times weekly.¹¹ The 2008 Hoffer study also described that patients receiving 1.5 g/kg excreted a mean 81.3±18.8 mg of oxalic acid (during and over the 6 h after infusion) before returning to baseline. Oxalic acid excretion normally ranges from 10 to 60 mg/24 h. Thus it was determined that a transient rise with subsequent return to normal shortly after IVC was not a threat to patients with normal kidney function. The study also found that patients reliably excreted 25% of the vitamin C during the infusions and established that time-blood plasma vitamin C concentration were relative and predictable according to dose of IVC.

The current study continues this work. The dose and frequency of IVC given is 1.5 g/kg administered 2-3 times weekly, though in this study it is given to patients receiving concurrent chemotherapy (not on the same day). It also reproduces similar, statistically analyzed minimal and transient rise in oxalic acid excretion during and after IVC, as well as a reduction in total ascorbate excreted after chemotherapy. It is plausible to consider that during pro-oxidant therapies, antioxidant blood levels may decrease. Body stores of vitamin C may be in flux, hence less may be excreted. Other investigators have conducted studies reporting that when given the same doses of IVC, patients with metastatic disease excrete less ascorbate compared to those with local disease.¹⁵ This phenomenon has been well-documented in other disease and chronic inflammatory states, as well as in smokers.¹⁶⁻¹⁸ It is thought that the higher state of inflammation in metastatic disease states consumes more antioxidants. That said, there is much concern over whether antioxidant vitamin C interferes with chemotherapy. Conventional oncology providers caution that in patients with known curative potential from conventional means, the addition of IVC therapy is an unknown and poses an undefined risk of interfering with the benefits of treatment until outcome studies prove otherwise. This is certainly something to further explore in well-designed studies. Most of the high dose IVC studies to date, including the Hoffer 2015 study and others referenced previously, are designed to test safety and benefits with advanced disease (eg, improving quality of life, stabilizing disease trajectory, lessening side effects of conventional therapies).
One interesting component of this study is that the authors report 2 cases of hypovitaminosis C out of 14 cases evaluated during enrollment. The odds of this occurring in cancer patients compared to the general population are higher. One observational study found 6 cases of scurvy in 3,723 consecutive patients treated for noncancerous conditions in a hospital emergency room; 6 cases of scurvy were found in 219 patients with cancer who were consecutively treated during the same timeframe. Informed clinicians should watch for signs and symptoms of hypovitaminosis and nutrient deficiency in patients with cancer. These symptoms may be commingled with signs of disease processes and side effects of standard antineoplastic treatments.

Cancer patients are known to have hypovitaminosis more frequently than healthy populations for a variety of reasons, such as physiologic stresses associated with disease processes, impaired oral intake, a history of surgery or radiation affecting absorptive digestive surfaces, and the catabolic effects of antineoplastic therapy.

Patients in this study also reported side effects of IVC—some of which the authors attribute to the high osmolarity and cooler than ambient temperature and/or sodium load of the IVC infusate. The authors state some of the side effects were reduced or eliminated with slowing the rate of the IVC infusion, reducing the total IVC dose, and/or letting the infusion solution come to room temperature before administration. It’s also notable that this study used sterile water and vitamin C for infusion vs sterile water, vitamin C, plus mineral additives.

Hoffer reports that adverse events or side effects may occur for patients using IVC unless safeguards and the above mitigating procedures are used. Appropriate screening as part of the methodology of this study includes G6PD testing of each patient prior to IVC administration and assuring adequate kidney function, since vitamin C is primarily cleared by the renal system. No further screening for safety with IVC is discussed in the methods section of the paper. However, other investigators have listed potential contraindications or exclusions in methodology such as serum glucose >300 mg/dL, hypercalcemia or hyper-oxaluria, metal storage diseases, and iron overload. This study reiterated the previous caution that finger stick glucose could be falsely abnormal and should be avoided for 12 hours after IVC.

This study adds to the safety literature on IVC in cancer care. It also provides objective, concise descriptive summaries of 14 cases of people with advanced cancer who received IVC adjunctive to standard of care chemotherapy. In a way, this brings forward the work of Cameron and Pauling, who reported on the treatment of advanced stage cancer patients who did not have the option of salvage therapies at that time period and were reported to have had improved quality of life and survival with use of IVC and oral vitamin C.

Though this prospective study by Hoffer et al is considered more methodologically rigorous in our current paradigm, the number of cases is too small to get an idea of what IVC might offer for patients in the day-to-day difficulties of managing disease and standard of care treatment. This study and the 14 case synopses, in which 3 people are reported to have longer than anticipated periods of stable disease deemed unlikely to result from chemotherapy alone, seems to convey rather more side effects from IVC with equal weighting to any benefits. In fact the study reports some rather significant-sounding side effects from high-dose IVC, as well as beneficial effects reported by patients. The QoL and mood questionnaires did not report any trends.

Hoffer relates that “despite its biological and clinical plausibility, [IVC] is ignored by conventional cancer investigators and funding agencies” and suggests that there may be value in an individual case-centered evaluation strategy such as “discovery in clinical practice,” which has been advocated as a means to discovering new indications for conventional drug therapies. The authors state that integrative cancer therapists prescribe IVC widely without collectively reporting clinical data that is normally gathered as important in cancer drug development.

Hoffer concludes “if carried out in sufficient numbers, simple studies like this could identify specific clusters of cancer type, IVC, and chemotherapy regimens in which unexpectedly...”
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beneficial outcomes or exceptional responses occur frequently enough to justify focused clinical trials.” This brings to mind the work being done in gynecologic cancers by Jeanne Drisko et al as was reported in the Ma 2014 study previously referenced. In my experience in working primarily with pancreatic cancer patients for several years in an integrative cancer hospital in which patients routinely received IVC as part of their care, this population is also of interest for further exploration in well-designed clinical trials. Perhaps IVC could be used adjunctively earlier in diagnosis and with first- and second-line regimens to test whether IVC combined with chemotherapy can improve survival outcomes vs standard therapies alone.

Many of us have seen through clinical experience that IVC appears to help quality of life and/or improve tolerability of standard chemotherapy regimens. Some of our patients have significant alteration in disease status and unusually favorable results when receiving IVC therapy alone or in addition to standard of care cancer treatment. If we can work to document cases like these via case reports or series and do the hard work of designing small clinical trials to test its benefits, as Hoffer’s 2015 IVC study advocates, we’ll improve our ability to learn about IVC and other therapies while helping create a new paradigm of integrative cancer care.

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Intake of Fish and Omega 3s and Breast Cancer Survival

Do polyunsaturated fatty acids improve mortality rates after breast cancer diagnosis?

By Keri Marshall, ND

REFERENCE

STUDY OBJECTIVE
The primary objective of this study was to explore whether dietary omega-3 polyunsaturated fatty acid (PUFA) intake from fish and other sources benefits survival after breast cancer in a group of women who were newly diagnosed with first primary breast cancer.

DESIGN
This is a follow-up study from a population-based study.

PARTICIPANTS
This study was conducted in Long Island, New York, among 1,463 women newly diagnosed with first primary breast cancer. Women were interviewed approximately 3 months after initial diagnosis to assess risk and prognostic factors, including dietary intake (using a food frequency questionnaire). The 2 primary diagnoses were a first primary in situ (16%) or invasive breast cancer (84%). At the time of diagnosis, women ranged in age from 20 to 98 years and 67% were postmenopausal; 94% identified their race as white, 4% as black, and 2% as other. This is reflective of racial distribution in the counties in which data was collected.

STUDY PARAMETERS ASSESSED
For this study, authors used resources from a population-based follow-up study conducted on Long Island, New York, among 1,463 women newly diagnosed with first primary breast cancer. Participants self-completed a food frequency questionnaire (FFQ) administered at baseline that assessed dietary intake for the year before the interview. PUFA intake from any dietary sources was estimated by linking participant responses from the FFQ (g/day for each food item), with the average nutrient values for foods available in the United States Department of Agriculture Database for omega 3 and 6 PUFAs. The following PUFA subtypes were estimated:

Omega 3
- Alpha linolenic acid (ALA)
- Eicosapentaenoic acid (EPA)
- Docosahexaenoic acid (DHA)
- Docosapentaenoic acid (DPA)

Omega 6
- Linoleic acid (LA)
- Arachidonic acid (AA)

An estimated total intake of omega 3 and omega 6 was calculated by summing each individual fatty acid within its respective category. Seafood consumption was also assessed by the FFQ and was differentiated by either being fish- or shellfish-based.

Other factors assessed included demographics, reproductive and menstrual history, exogenous hormone use, family history of breast cancer, body size, physical activity, alcohol and cigarette use, occupational history and environmental exposures, and other basic medical history.

PRIMARY OUTCOME MEASURES
Vital status was determined through December 31, 2011, yielding a median follow-up of 14.7 years and 485 deaths, 210 of which were breast cancer–specific. Participants’ deaths were determined via a linkage with the National Death Index, a standard epidemiologic resource used for attaining mortality data. Women were identified who died from all causes (death from any cause) and also women who died from breast cancer specifically.

In the statistical analyses, quartiles were created for PUFA exposure (total PUFA, total omega 3, ALA, EPA, DHA, DPA, total omega 6, LA, ALA, and the ratio of omega 3 to omega 6.) In Cox proportional hazard models, there was also consideration between total omega 3 and 6 intakes and between the omega 3/6 ratio in association with mortality. Effect modification of the association between PUFA intake and mortality by menopausal status, hormone receptor status, dietary supplement use, treatment, and BMI were also examined in PUFA regression models.

KEY FINDINGS
In this population-based study of women with breast cancer in Long Island, New York, there was an observed reduction of 16% to 34% in all causes of mortality after 15 years of follow-up for women with a diet high in fish and the long-chain PUFAs EPA, DHA, and DPA. Based on the FFQ responses, on average women had a total omega 3 intake of 0.99 g/day, with ALA intake being the highest contributor with an average of 0.85 g/day. Average omega 6 intake was much higher, with an average 7.51 g/day. LA was the highest contributor at an average intake of 7.44 g/day. Fish was the primary contributor to the high intake of long-chain omega 3 PUFAs, while foods like muffins, biscuits, and fried foods contributed to the shorter-chain omega 3 ALA. A diet high in omega 6, specifically AA, was linked to foods such as eggs and meat.

Statistical analysis indicated that survival was improved in women with breast cancer who reported a higher intake of the long-chain omega 3s EPA, DHA, and DPA (quartiles 3 and 4) compared with those in the lower quartile. Fish intake specifically was associated...
with a 25% to 34% reduction in all-cause mortality. Separately, lower rates of death were observed for those in the highest quartile of tuna intake compared with those with no intake and compared to the highest quartiles for other fish intake (brolled/baked). There was no evidence of association for all-cause mortality and shellfish intake. Adjusted estimates for breast cancer–specific mortality demonstrated a pronounced reduction (19%) when tuna and other fish intake was assessed in relation to 5 years of follow-up. There did not appear to be an observed relationship with the omega 3/omega 6 ratio and outcome measures.

PRACTICE IMPLICATIONS

This study appears to be the first study to examine a potential relationship between PUFA intake and breast cancer survival. Naturopathic doctors and other integrative practitioners routinely change their patients’ diets as a foundational element of a treatment plan, particularly in individuals with a cancer diagnosis. This study provides evidence to support the addition of foods with omega-3 fatty acids, both shorter- and longer-chain, to provide some risk reduction for all causes of mortality in women with a history of breast cancer.

The omega-3 foods in this study were from both marine (seafood) and nonmarine sources, although fish appeared to be most beneficial. A healthy, balanced diet should consider both. Foods naturally higher in preformed long-chain PUFAs, such as EPA and DHA, include fatty fish such as salmon and tuna. While this study did not look specifically at dietary supplementation, preformed EPA and DHA can also be found in fish oil, krill, and algal oil supplements and should be considered for those who do not eat fish.
Agaricus bisporus Mushroom in Biochemically Recurrent Prostate Cancer
Review of a recent phase I trial

By Sara Thyr, ND

REFERENCE

DESIGN
This was a phase I, single-arm, unblended, single-facility trial.

PARTICIPANTS
The 36 male patients enrolled (mean age 68) all had been diagnosed with biochemically recurrent prostate cancer (BRPC). All had had prior radiation therapy, and 33 (92%) had also undergone earlier prostatectomy. Eleven patients (30%) also had undergone hormonal therapy. Their mean prostate-specific antigen (PSA) at the onset of therapy was 1.9 ng/ml. To be included in the study, patients had to demonstrate biochemical evidence of treatment failure through increasing PSA levels. They were excluded from the study if they showed clinical or radiographic evidence of metastatic disease.

INTERVENTION
Patients were given white button mushroom (WBM) powder tablets twice a day until PSA progression, clinical progression, or toxicity. Six patients were separated into 6 mushroom dose cohorts: 4, 6, 8, 10, 12, and 14 g/day. If no patient among the dose cohort exhibited dose-limiting toxicity during a 28-day treatment cycle, the next higher dose was tested.

OUTCOME MEASURES
The primary objective was to evaluate treatment feasibility and associated toxicity. The secondary objectives were to determine WBM's effect on serum PSA/androgen levels, myeloid-derived suppressor cells (MDSCs), and cytokine levels.

RESULTS
No study participant experienced dose-limiting toxicities. Four of the participants had a partial or complete response to the mushroom powder for an overall PSA response of 11% (95% confidence interval: 4%-26%). Two patients (at dosages of 8 and 14 g/day) experienced a prolonged complete response in which their PSA declined to undetectable levels and remained undetectable at least to the date when the article was submitted for publication, a response of 49 and 30 months. Two patients demonstrated a partial response in which their PSAs dropped to 50% of baseline. One of these patients had remained on the study for 39 months. The second partial responder maintained the decreased PSA for only 7 months. Five other patients showed no increase in PSA for the duration of the study. In addition to these partial and complete responders, 13 patients (36%) demonstrated some PSA decline after beginning therapy.

IMMUNOLOGICAL FACTORS
No definitive cytokine patterns were noted except for that of interleukin-15 (IL-15). Complete and partial responders had higher IL-15 levels at the beginning and after treatment. Overall IL-15 levels were not changed by treatment in the responders and nonresponders.

PRACTICE IMPLICATIONS
This article should bring a small ray of optimism to those with biochemically recurrent prostate cancer (BRPC). While these mushroom tablets do not work all of the time, they work some of the time.

BRPC is defined by an increase in PSA in men who have already had definitive treatment for prostate cancer. Treatments included prostatectomy and/or radiation. In this study most of the participants had undergone both treatments.1

Within 10 to 15 years of therapy, 25% to 30% of all prostate cancer patients experience recurrence.2 Most of these study participants had already been treated with both surgery and radiation, leaving them few if any additional expectations for possible cure. In this setting of biological recurrence, the primary option offered will be androgen deprivation therapy. This choice will suppress prostate cancer, but it is not considered curative and typically is accompanied by significant undesirable side effects. These include “weight gain, muscle weakness, hot flashes, erectile dysfunction, loss of libido, increased risk of diabetes, and cardiovascular problems.”2

Androgen deprivation therapy also does not represent a potential cure, but rather a delay of disease recurrence. Its effect on overall survival is not clear. Because of this, the authors felt that it was worth investigating the potential of a minimally toxic oral therapy administered on an outpatient basis for BRPC that shows effectiveness against disease progression.

Mushrooms are not the only naturally occurring substances to affect the growth or spread of cancers. Several natural therapies have shown some promise in prostate cancer prevention, recurrence, and treatment, including pomegranate juice,3 modified citrus pectin,4 lycopene, and isoflavone.5 Yet none of these substances has been reported to reduce PSA to the extent seen in this trial.

Mushrooms have been used medicinally for centuries, and many species have been shown to have anticancer properties.6 Mushroom has been shown to inhibit prostate cancer, colon cancer, and breast cancer cell lines.7 The authors of this current study are well known for earlier research demonstrating that WBMs act as aromatase inhibitors in women.8,9 In this paper they use their assay of aromatase inhibition to judge the potency of their mushroom powder.
THE WHITE BUTTON MUSHROOM

The mushroom used in this study—the white button mushroom (Agaricus bisporus) is the most common edible mushroom available in the United States. It is widely cultivated and readily available in grocery stores. Over half a billion pounds are cultivated annually in the United States. Evidence is mounting for the beneficial anticancer effect of the WBM. Isolated lectins have been shown to help chemotherapy for breast and colon cancer work more effectively by increasing the sensitivity of the cells being treated to the medication. They also decrease the proliferation of colon cancer cells and increase antioxidant function. Breast cancer cell proliferation was decreased because of inhibition of aromatase activity into WBM and some of its fractions, including conjugated linoleic acid. Prior research of WBM on prostate cancer cell lines proved that WBM extract inhibits cell proliferation largely by inducing apoptosis. It was because of this promising earlier research that the current trial was conceived.

This study was to evaluate the feasibility, toxicity, and biological activity of prolonged treatment with WBM powder. By looking at immune modulators, cytokines, and MDSCs, the authors wanted to also find any biological differences between those patients whose PSA responded and those whose did not.

IMMUNOSUPPRESSIVE CELL SUBSET

MDSCs in peripheral blood from enrollment to week 13 were decreased in the patients who had complete and partial responses. Their levels dropped 78%, 45%, 94%, and 65%. There was no change in MDSCs in non-responders.

While IL-15 is studied on its own for cancer, it might not be ideal for single treatment. In these patients, it looks like the WBM strongly influenced the immune inhibition. Along with this, MDSCs play a role in inhibition of the immune system, and their reduction seems to unleash stronger cancer surveillance. MDSCs were dramatically reduced in the strongest responders. Recall that these men had the highest IL-15.

While WBM lowers blood sugar and cholesterol in diabetic and hypercholesterolemic rats, significant changes in blood glucose and lipids have not been seen with humans treated with WBM.

LIMITATIONS

With just 36 patients enrolled, this study was relatively small. Repeating this dosage of WBM in a randomized, placebo-controlled setting is necessary to make a more definitive conclusion.

In addition, much research on medicinal mushrooms uses hot water extracts as the preparation method of choice, since mushrooms are very high in chitin, which is difficult for the human body to break down and utilize. The authors’ initial research on WBM studied the aromatase activity of the water extract of the mushroom. But since for this study they utilized lyophilized (freeze-dried) whole WBM, it is unclear which aspect of the mushroom they were looking to assess and which component is the most beneficial for BRPC. In fact, it does not appear that aromatization was affected, since measurements of testosterone, dihydrotestosterone (DHT), and dehydroepiandrosterone (DHEA) throughout the study were unchanged. Future studies should include an arm for the freeze-dried mushroom as well as a hot water–derived extract, in order to compare them. It would also be worthwhile to assess which of the components with known medicinal activity were highest in the mushrooms used, and which were likely most beneficial in treatment. The mechanism of action for lowering the PSA in this study is unknown.

Mushrooms tend to readily absorb both nutrients and toxic elements from their growth media. Therefore being aware of any toxic elements in the growth media is critical. The supplemental materials showed a very thorough analysis of potential toxins, including arsenic, lead, and cadmium, as well as some biological contaminants like E. coli and Salmonella, all of which were negative.

REFERENCES

**REFERENCE**

**DESIGN**
A prospective, randomized, crossover trial in breast cancer patients receiving antihormonal treatment

**PARTICIPANTS**
A total of 46 patients were recruited for the study but only 31 completed both phases, the majority dropping out during the pollen phase because they found the taste of the pollen mixture unpleasant. Mean age of participants was 60.8 years.

All participants had completed surgery for breast cancer and had been on antihormonal therapy for at least 3 months before the study. Exclusion criteria included distant metastases, pregnancy, allergy to bee pollen and/or honey, concomitant disease, psychiatric disease, use of other treatments for menopause symptoms, or an inability to read German.

**STUDY MEDICATION AND DOSAGE**
Patients received 1 tablespoon a day of either a mixture of pollen and honey (pollen group) or pure honey (honey group) for 2 weeks. After a washout period participants received the alternate treatment for an additional 2 weeks.

**OUTCOME MEASURES**
Menopausal complaints were assessed using the Schneider and Heinemann Menopause Rating Scale (MRS). Blood samples were collected at each stage of the study and tested for triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and estradiol.

**KEY FINDINGS**
All patients reported significant improvements during the study: 68.3% of patients receiving honey and 70.9% of patients while receiving pollen. The differences between groups were not significant; both honey and pollen relieved menopausal symptoms caused by adjuvant treatment of breast cancer. These improvements were noted 3-4 days after initiation of treatment regardless of whether patients received tamoxifen or an aromatase inhibitor, or were in the honey or the pollen groups. Patients receiving pollen and taking tamoxifen showed a trend toward higher rates of improvement (86.7 vs. 58.8%), but this difference was not significant. No differences in serum cholesterol, triglycerides, or estradiol were seen. Patients taking aromatase inhibitors experienced significantly more improvement of symptoms compared to patients treated with tamoxifen. There was also a trend toward an increase in estradiol levels by honey in patients receiving aromatase inhibitors.

**PRACTICE IMPLICATIONS**
Suggesting to patients with menopausal symptoms secondary to adjuvant treatment of breast cancer that they try taking a tablespoon of honey once a day for a week or so as a clinical experiment sounds almost too simple, but it is certainly worth a try.

Finding ways to relieve menopausal symptoms is clinically important as many breast cancer patients will discontinue treatment rather than experience the discomfort of hot flashes. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial reported discontinuation rates of 14.3% for tamoxifen and 11.1% for anastrozole. Providing relief may increase compliance with these currently accepted therapies.

In the past we have advocated for a range of alternative supplements to relieve menopausal symptoms, including vitamin E, soy, black cohosh, flax, and red clover. Questions have remained about the safety of those that employ phytoestrogens and whether they may stimulate breast cancer growth. Chi et al’s 2013 meta-analysis of soy and breast cancer suggests that at least in the case of soy, the phytoestrogens are protective.

Several papers have reported that pollen extracts were useful in treating hot flashes, but this may be the first to suggest that even plain honey was useful. In this case honey was used as a placebo against which to compare the active pollen and honey mixture.

While some placebo effect was possible, the researchers suggest that the improvements seen greatly exceeded the 25% response rate that would have been predicted from placebo effect.

Tualang honey, a rare form of wild honey produced by Asian honeybees from jungle floral nectars, may have an estrogenic effect. The “common” honey used in this menopausal study, and the kind we eat, is produced by European honeybees (*Apis mellifera*). Tualang honey is produced by *Apis dorsata* bees that nest in Tualang trees. This Tualang honey has in fact been suggested as a means to prevent osteoporosis.

So although for unknown reasons the Tualang honey may somehow stimulate estrogen production, at this point there is no reason to think that common table honey does the same. It is unfortunate that Tualang honey is not yet readily available.
available to our patients. Tualang honey has been reported to augment the effect of tamoxifen against breast cancer cells\(^8\) and so might be helpful if consumed.

Note that there was a trend toward increased estrogen levels in the honey group, but this association did not reach significance. If this association proves true, it will no doubt trigger debate as to whether breast cancer patients should consume or abstain from honey.

While a rationale for a mechanism of action remains to be found for honey’s reported benefit, there is little reason to justify not attempting to employ it clinically. In this report honey worked better in women taking aromatase inhibitors and it took only 3-4 days of regular honey use until improvement was felt. The downsides of honey supplementation are negligible, so there is no reason to not try this in practice.

REFERENCES
Exercise During Cancer Treatment Lessens Fatigue
Combating the most common side effect of cancer treatment

By Tina Kaczor, ND, FABNO

REFERENCE

DESIGN
Two arm, randomized controlled trial

PARTICIPANTS
Women undergoing, or scheduled to undergo, treatment with chemotherapy for newly diagnosed breast cancer. Recruitment took place at 7 facilities throughout the Netherlands between January 2010 and December 2012.

Participants were randomly assigned to either the exercise group or to “usual care.” All participants began the study within 6 weeks of diagnosis. A total of 204 participants were recruited: 102 in the exercise group and 102 in the “usual care” group. There were 15 participants lost to follow-up in the intervention group and 25 in the control group, leaving 87 and 77 evaluable women in each group, respectively, at week 36.

INTERVENTION
An 18-week, individualized exercise program versus “usual care,” where the patients were asked explicitly not to partake in more exercise than their usual activities of daily living. Those in the intervention group underwent a personalized assessment and individualized exercise sessions twice weekly with a physiotherapist at the treating institution. Each session was 60 minutes total and included 5 minutes of warm-up, 25 minutes each of aerobic and resistive exercise, and 5 minutes of cool down. Each session also included cognitive behavioral therapy as part of the visit. Those in the intervention group were also asked to engage in a minimum of 30 minutes of unsupervised exercise 3 days per week in addition to the formal sessions.

The control group was asked to maintain usual physical activity levels from the start of the study through week 18. At week 18, those in the usual care group were allowed to participate in exercise programs that are part of “usual care” for everyone who has gone through cancer treatment in the Netherlands.

OUTCOME MEASURES
Fatigue was the primary outcome measure. Assessments for fatigue were made at baseline, 18 weeks, and 36 weeks. The Multidimensional Fatigue Inventory (MFI), which includes a 20-item questionnaire measuring general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue was used. The Fatigue Quality List (FQL), which consists of 28 adjectives in 4 subscales, was used to further assess perception of fatigue.

Quality of life (QoL) was measured using the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and the 36-item Short Form Health Survey (SF-36). Anxiety and depression were assessed using the 20-item Hospital Anxiety and Depression Scale.

Physical activity outside the study setting was evaluated with the Short Questionnaire to ASess Health enhancing physical activity (SQUASH) form.

Aerobic capacity was assessed using cardiopulmonary exercise test with continuous breathing gas analysis. Thigh muscle and handgrip strength were measured using dynamometers. Body height and weight were measured.

KEY FINDINGS
Baseline: The study group characteristics were comparable by most measures, except women in the intervention group were more highly educated (46.1% vs 35.3%), had more triple negative breast cancers (23.5% vs 11.8%), and were more likely to be postmenopausal (44.1% vs 32.4%).

18-week assessment: The study found that exercise that began within 6 weeks of diagnosis significantly reduced the amount of physical fatigue developed during conventional cancer treatment. General and mental fatigue also trended toward less severe in the intervention group but did not reach statistical significance. Submaximal cardiorespiratory fitness and muscle strength (leg extension and flexion) were also significantly better with exercise intervention.

36-week assessment: There was no difference between groups in any parameters measured at 36 weeks. Most of the control group began to exercise posttreatment as part of the “usual care” offered by the healthcare system in the Netherlands.

Body weight was increased at 18 weeks and 36 weeks for both groups with no difference between groups. There was no difference at 18 or 36 weeks in overall quality of life, anxiety, or depression.
COMMENTS & COMMENTARY

Fatigue is the most common side effect reported by those receiving conventional cancer treatments (chemotherapy and/or radiation). Several reviews and meta-analyses have suggested exercise during and after treatment results in fewer fatigue symptoms. It is passé to suggest to patients with breast cancer undergoing chemotherapy to “just take it easy and rest.” The evidence clearly suggests that movement/exercise during treatment is beneficial.

There are, however, questions about how much and what types of exercise are best. While ongoing studies will more precisely define these details, we have enough data to date to give some solid guidance to our patients.

A Cochrane review published in 2012 determined that aerobic exercise during and after treatment for solid tumors lessened fatigue, but there was insufficient evidence to determine whether resistive exercise was helpful. Note that the review did not conclude resistive exercise is not helpful, merely that there was insufficient evidence to make any conclusion.

A Cochrane review is the most rigorous in today’s evidence-based medical paradigm. It is safe to say there is little doubt that partaking in aerobic exercise during and after treatment leads to improvements in quality of life for those undergoing treatment for breast cancer.

Resistive exercise has only recently garnered attention in clinical research. Since the 2012 Cochrane review, several studies have suggested resistive exercise during treatment may be beneficial. Most of these trials have been well designed to minimize the psychosocial influences inherent to group activities such as exercise classes. In some fashion, the trials divided participants into 2 groups and used a supervised group activity, such as relaxation, as the control. This allows some mitigation of the confounder of social support, which may be therapeutic in itself. This design is not relevant to the study reviewed here, since participants were seen 1-on-1 with a physiotherapist.

Clinical trials of resistive exercise in women undergoing radiation and/or chemotherapy for breast cancer are ongoing. This is happening at a time when there is a growing understanding of how muscle itself influences systemic physiology. No longer is muscle just a mechanical contributor to overall health. In nonobese adults, muscle is the largest endocrine organ. In obese adults, adipose can be the largest endocrine organ. By definition, endocrine organs are those that produce and secrete molecules that have effects on distant organs/systems. Muscle cells produce and secrete myokines.

The secretion of myokines is highest during the act of muscle contraction. Myokines then act locally (autocrine/paracrine) or systemically (endocrine). The endocrine effects of myokines appear to be at the crux of how exercise ultimately lowers the risk of many chronic diseases. The discovery and continuing elucidation of myokines offers a new paradigm for understanding how exercise in general, and muscle contraction specifically, can influence overall physiology so profoundly.

Myokines include well-known molecules such as interleukins (eg, IL-6, IL-4, IL-15), insulin-like growth factor-1 (IGF-1), fibroblast growth factor, and many others. In addition, the muscle produces some more unique molecules such as irisin. Irisin is partly responsible for the simulation of cortical bone growth with exercise. Such factoids have practical use for us as clinicians as means of motivating our female patients, especially those on aromatase inhibitors, to stimulate bone growth with exercise.

It appears that a combination of aerobic and resistive exercise, as was used in the study currently under review, is optimal for those undergoing treatment for breast cancer. However, the optimal exercise intensity may vary depending on whether the patient is in active treatment (chemo/radiation) or posttreatment. A pooled analysis of 17 studies of breast cancer patients undergoing conventional treatment showed that low- to moderate-intensity exercise during treatment was more beneficial than higher-intensity exercise. In contrast, the opposite has been found true posttreatment: Greater intensity reaps greater the benefit. This is not surprising given the physical stress the body is under during chemotherapy/radiation. Treatment induces a higher oxidative and inflammatory state. High-intensity exercise is itself a mild stressor on the body, also creating oxidation and transient inflammation, so it stands to reason that during treatment the additive effects of high-intensity exercise may be excessive.

A final consideration: Exercise during and after treatment may also lessen the risk of recurrence. A meta-analysis published in 2012 that culled the medical literature from 1950 to 2011 determined that exercise not only improved quality of life, but also was associated with a 25% to 75% reduction in risk of death from breast cancer specifically. Such information can be highly motivating for patients and can lead to better compliance than blanket statements about the overall benefits of exercise.

There seems to be little if any down side risk to exercising within one’s physiological limits during treatment. We, as clinicians, should motivate patients to prioritize exercise above nutritional supplements and above adopting a pristine diet. Adding a structured resistive exercise program to the aerobic component will likely lessen fatigue during treatment and lead to overall improvements in quality of life.
REFERENCES


