EPEC-O

Education in **P**alliative and **E**nd-of-life **C**are - **O**ncology

Participant's Handbook

Module 3b:

Symptoms – Anorexia/ Cachexia

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Case*

J.F. is a 56-year-old engineer who presents with low-grade, constant epigastric pain, increasing fatigue, an eight pound weight loss over the past two months, and change in appetite associated with a sense of 'constantly being full.' A diagnosis of cancer of the pancreas with liver metastases is established. J.F. agrees to enter an experimental chemotherapy trial. In addition, he and his family ask for a dietitian consult.

* This case is not on an EPEC-O Curriculum trigger tape.

Introduction

Anorexia is a *lack or loss of appetite*. Cachexia is a *wasting syndrome characterized by loss of muscle and fat directly caused by an aberrant host response to cancer*.[1] Cachexia, with rare exception, is accompanied by anorexia which is also caused by many of the same factors that cause cachexia. The syndrome occurs in the majority of patients with advanced, refractory malignancies. The signs and symptoms of the anorexia/cachexia syndrome include loss of lean tissue, a decline in performance status, fluctuations in resting energy expenditure, and loss of appetite.[2,3,4,5]

Anorexia/cachexia caused by cancer is distinct from secondary anorexia/cachexia. The latter grouping contains a set of often correctable problems including emotional disorders, infections, pain, obstruction, constipation, and other symptoms which independently can reduce appetite, weight, and strength.

Two aspects of cancer-related anorexia/cachexia deserve special comment. First, body composition assessment shows that these patients lose a disproportionate and excessive amount of lean tissue.[2] Although weight-losing cancer patients lose both fat and lean tissue, it is the loss of lean tissue, particularly skeletal muscle, which is most profound. Secondly, aggressive feeding does not reverse the cancer anorexia/weight loss syndrome. For example, multiple studies that examined the role of total parenteral nutrition in cancer patients found no clinical benefits.[6,7] Evidently the cancer anorexia/weight loss syndrome is a result more than the absence of sufficient nutrition.

Anorexia/cachexia has a devastating effect on family life. As functional capacity is lost, patients become increasingly dependent on family, friends, and institutions. Health care costs dramatically increase in pace with family anguish. Sharing a meal is a cornerstone of family life; friends and family also suffer as they daily observe the wasting of a loved one.

In addition to psycho-social distress, anorexia/cachexia limits therapeutic options. Weight loss correlates with treatment toxicity and poor tumor response. Recent studies suggest that inflammatory cytokines associated with primary anorexia/cachexia interfere with hepatic medication metabolism and may even directly or through induction of acute phase proteins block chemotherapeutic anti-tumor effects.[8,9]

Prevalence

Anorexia/cachexia and the frequently associated problem of fatigue are among the most common symptoms encountered in patients with advanced cancer. In some malignancies, notably non-small cell lung cancer, pancreas, and upper gastrointestinal cancers, weight loss is often present at first diagnosis. Patients with cancers not characterized by early onset of cachexia, eg, breast, lymphomas, colorectal cancer, may experience the syndrome in their last weeks of life.

Prognosis

Loss of greater than 5% of premorbid weight prior to chemotherapy predicts death.[3] This is independent of disease stage, tumor histology, and patient performance status. There is also a trend towards lower chemotherapy response rates among weight-losing cancer patients. Anorexia is also a powerful predictor of early death.[10] Patients with a loss of appetite have a far worse prognosis compared to those who maintain their appetite. This observation persists even after adjusting for several other prognostic parameters. Thus, both weight loss and anorexia predict a poor prognosis for patients with advanced cancer.

Pathophysiology

Cachexia is not due to reduced nutritional intake. Enteral/parenteral feeding does not reverse the syndrome. Associated metabolic abnormalities often precede rather than follow initial weight loss.

The anorexia/cachexia syndrome is a multi-factorial entity. While the association between contributing factors is not clearly understood, chronic inflammation has been identified as a core mechanism.[11] Lipolysis, muscle protein catabolism, increases in acute phase proteins (including C-reactive protein) and a rise in pro-inflammatory cytokines (notably IL-1, IL-6, TNF Alpha, and leukemia inhibitory factor) are associated with the syndrome and are similar to the metabolic response to an acute injury.

Malignancies produce chemicals that also contribute to cachexia in some patients. Both lipolytic and proteolytic substances have been discovered in rodents and humans.[12,13] Some tumors also directly produce inflammatory cytokines.[14] Raised basal metabolism, changes in autonomic control mechanisms (favoring increased sympathetic activity), and alterations in hormone production, eg, reduced testosterone levels, are often observed.[15,16] The interaction between chronic inflammation, tumor cachectic products, and other associated pathophysiologic features is unclear. The panoply of abnormalities suggests common root causes with a cascade of imbalances within the neuro-hormonal immune axis. There is not yet one mediator of the anorexia/cachexia syndrome which clearly explains all its features. Inflammatory cytokines, specifically tumor necrosis factor alpha (TNFα), interleukin-1 beta, interleukin-6, as well as others, may be playing a causative role.[17,18,19,20,21,22,23,24]

Anorexia may be due to the effects of inflammatory cytokines on the hypothalamus with consequent changes in the balance of neuro-transmitters stimulating or inhibiting food intake. Neuropeptide Y and Agouti Related Peptide (AGRP) are appetite stimulating neurotransmitters; conversely the Opio-melanocortin and the Cocaine Amphetamine Related Factor (CART) neurotransmitter systems inhibit food intake.[25,26] The 'Yin' and 'Yang' of appetite depend on the interplay between these two forces. In health, leptin, produced in fatty tissue, increases inhibitory activity, while ghrelin, a hormone mainly produced in the stomach, stimulates appetite; both act through their influence on the above neurotransmitter systems. These physiologic regulators seem overwhelmed in cachectic patients; leptin levels are low, ghrelin levels high, but all to no avail.[27] The afferent loop of the appetite-satiety cycle, as described above, is better understood than the efferent loop. Relatively little is known about the translation of hypothalamic drive to energy intake and processing.

Assessment

At the first patient contact, record weight, appetite, and factors affecting food intake. Note variations in taste and smell (commonly disturbed), swallowing, and evidence of early satiety. As patients are subject to many secondary problems contributing to anorexia/cachexia physicians may use an 'aide-memoir' to ensure these problems are covered (see Table 1).

The profile of factors causing anorexia/cachexia no doubt varies from patient to patient. Moreover, genetic background may influence cachexia risk and response to therapy.[28] While an etiology based anorexia/cachexia classification system would be helpful, it remains to be defined. Definitive studies on genetic disposition are also awaited.

Specific biochemical markers of the anorexia/cachexia syndrome are not available, but less specific markers may be helpful. Patients with primary anorexia/cachexia usually have a low serum albumin and high C-reactive protein (CRP) (increasing levels of CRP provide a rough measure of chronic inflammation). Commonly, they are anemic with decreased lymphocyte counts. Symptoms of early satiety may be linked to abnormalities in autonomic function such as tachycardia.[28]

In a weight losing patient with a normal albumin and a normal or slightly elevated CRP, the physician should be particularly alert for alternate causes for weight loss.

Table 1. An approach to identify potentially correctable causes of cancer cachexia

This assessment is made easier by the routine use of simple patient-completed questionnaires. These allow for ongoing quantitative data that helps physicians 'zero in' on specific problem areas. Examples of such scales include the Edmonton Symptom Assessment Scale,[29] the EORTC quality of life questionnaire (QLQ C-30) and its associated diseased specific modules,[30] and the Edmonton Functional Assessment Tool.[31]

Potentially correctable problems	Possible approaches
Psychological factors: Anxiety	Anxiolytics
Depression	Anti-depressants
Family distress	Social assistance
Spiritual distress	Counseling
Eating problems: Appetite	Referral to a nutrition clinic or a dietitian
Disturbed taste or smell	Zinc supplementation
	Multi-vitamins
Oral: Dentures, mouth sores	Anti-fungal medication
Thrush	Oral moisteners
Dry mouth	Change medications
Swallowing difficulties	Anti-fungal medication
	Esophageal dilation
	Regurgitation therapy
Stomach: Early satiety	Gastric stimulants
Nausea and vomiting	Related to cause
Bowel: Obstruction	Related to cause
Constipation	Laxatives, especially if on opioids
Malabsorption: Pancreas	Pancreatic enzymes
Fistulas	Related to cause
Fatigue: Inability to sleep	Anxiolytics
	Exercise protocol
	Sleep protocol
Motivation	Exercise protocol
	Methylphenidate
Function	Exercise protocol
	Cause related
Pain	Appropriate analgesics
	Nerve blocks: surgical, percutaneous
	Counseling
Metabolic: Diabetes	As indicated
Adrenal insufficiency	Steroid replacement
Hypogonadism	Testosterone
Thyroid insufficiency	Thyroid replacement

Management

Before embarking on management for this syndrome, ask the following questions:

- Does this patient have any reason other than the known cancer for weight loss, such as bowel obstruction or mucositis or another mechanical reason to explain this weight loss?

If this is the case, the use of an appetite stimulant would be inappropriate and treatment of the mechanical problem should be the main focus.

- Does this patient really want an appetite stimulant?

Progestational agents and corticosteroids improve appetite and result in weight gain, but they fail to augment lean tissue, improve global quality of life, or improve survival. If appetite stimulation as the singular goal of therapy is important for the patient, or the family, there may be a role for improving appetite.

What does not work

Feeding patients, either enterally or parenterally, does not reverse or slow the cancer anorexia/weight loss syndrome or improve appetite. In 1989, the American College of Physicians addressed the role of total parenteral nutrition in patients with advanced cancer receiving chemotherapy and radiation with the following statement: [32]

> 'the routine use of parenteral nutritional for patients undergoing chemotherapy should be strongly discouraged.'

Similarly, dietary counseling does not improve patient outcome.[33] Therefore, attempts at increasing caloric intake do not reverse the cancer anorexia/weight loss syndrome.

What works

Treat reversible causes (see Table 1) such as anxiety-depression, oral thrush, constipation, poorly controlled pain and early satiety, each of which, if present, strongly influences appetite, motivation, and mobility.

Anorexia

Strong evidence suggests that corticosteroids and progestational agents are effective at improving appetite if appropriate doses are used. [34,35]

Corticosteroids

The relative efficacy of various corticosteroids is also thought to be equivalent. Dexamethasone is often selected because of its absence of mineralocorticoid effects. Dexamethasone has been demonstrated to improve appetite on a short-term basis in

patients with advanced disease.[36] Subsequent placebo-controlled clinical trials have replicated this finding.[33] A common dosing regimen is:

- Dexamethasone 2-8 mg PO q AM

While corticosteroids increase appetite, they are catabolic and reduce muscle mass and function. Appetite stimulation is usually transient, and ceases to be helpful after 3-4 weeks. Moreover, fluorinated corticosteroids, eg, dexamethasone, are particularly prone to cause muscle breakdown. Long term use is therefore not recommended in mobile patients. If longer term use is deemed necessary, consider switching from dexamethasone to an alternate corticosteroid, eg, prednisolone. A common dose range is:

- Prednisolone dosing 20-40 mg PO q AM

Progestational agents increase appetite and weight in 35-60 % of patients. Megestrol acetate is the best studied progestational agent.[35,37] Megestrol acetate oral suspension has gained popularity because of its improved bioavailability. There is, however, a significant food effect. The medication is best absorbed when taken along with a high fat meal.[38]

- Start with megestrol acetate 400 mg/day. If appetite has not improved within approximately 2 weeks, escalate to megestrol acetate 600 – 800 mg/day.

The length of response to megestrol is longer than with corticosteroids. The weight gained is primarily as fat (not a bad outcome in its own right). A recent geriatric study suggests that megestrol also has catabolic effects on muscle.[39] Adrenal suppression may also occur as with any agent with glucocorticoid effects.

The mode of action of corticosteroids and progestational agents is not fully established. They both reduce the production of inflammatory cytokines. Whether direct positive efforts on the hypothalamic feeding centers occur is not certain.

Both megestrol acetate and dexamethasone are relatively well tolerated overall. There is a slight risk of thromboembolic episodes with megestrol acetate. This risk is higher in patients receiving concomitant chemotherapy. A history of thrombophlebitis is a relative contraindication for prescribing megestrol acetate or another progestational agent. Patients on megestrol acetate may need to receive corticosteroid repletion in the face of serious infections, trauma, or surgery because of the adrenal suppression.[40]

In contrast, dexamethasone puts patients at risk for myopathy, cushingoid body habitus, and peptic ulcer disease.[33] These side effect profiles play some role in determining which agent might be better for a specific patient.

In general, patients with a life expectancy of a few months or more may do better with megestrol acetate. Those with a life expectancy of only a few weeks, or those with a history of thrombophlebitis, may be able to get by with dexamethasone, as they are less likely to suffer side effects from corticosteroids in the short term.

Cannabinoids

Cannabinoids are known to give healthy people the 'munchies.' Some evidence exists for their use in anorectic cancer patients. More success may be seen in people familiar with the effects of marijuana (where an adverse psychotomimetic event may be viewed as a side benefit) although cannabinoid naïve patients may also benefit. Extant studies support the use of a marijuana congener, dronabinol. Claims are made that smoked marijuana is particular efficacious; proof is awaited. Endogenous cannabinoids are present in the brain. Most receptor activity is noted in 'hedonistic centres' such as the nucleus accumbens, with lesser hypothalamic activity.[41] Marijuana may, in some part, directly act on the hypothalamus, although its major appetite effects may depend on its activation of the centres mediating pleasurable eating experience.

Increase gastric emptying

Patients may attribute their poor appetite to 'feeling full,' either all of the time or shortly after eating. Early satiety may stem from abnormal hypothalamic signals and/or autonomic abnormalities with consequent delay in gastric emptying. Metoclopramide and domperidone may relieve early satiety through stimulation of gastric emptying. The fourteen ring macrolide antibiotics, eg, erythromycin and clarithromycin, also stimulate gastric emptying. Their use in cancer patients has only been studied in a few small Japanese trials.[42]

- Metoclopramide, 10–20 mg PO q 6 h (ac & HS)
- Domperidone 10–20 mg PO q 6 h (ac & HS)

Pharmacological agents for the cancer anorexia/weight loss syndrome have been tried. Among the medications that have been tested (see Table 2) and those that require further testing (see Table 3), two classes of agents stand out for their efficacy: progestational agents and corticosteroids.

Table 2: Agents tested that do not benefit anorexia/cachexia syndrome
Cyproheptadine
Dronabinol
Eicosapentaenoic acid
Fluoxymesterone
Hydrazine sulfate
Pentoxifylline

Table 3: Potentially effective agents that require further study
Adenosine triphosphate
Creatine
Oxandrolone
Thalidomide
TNF alpha inhibitors

Cachexia

Can we increase appetite and sustain muscle? Only recently has this question been addressed. Results from small trials are encouraging but not definitive.

Muscle maintenance is dependent upon: 1) an adequate supply of efficient nutrients, 2) the processing of energy sources, and 3) the normal balancing of muscle synthesis and proteolysis. Based on this triad, a variety of single-agent trials have recently reported promising results.

Anabolic agents – androgens

Athletes have known for years that androgens build muscle. The medical profession has been slow to turn this observation to patient advantage, possibly because of the stigma associated with medications of abuse or because of adverse event concerns.

Fluoxymesterone can increase appetite, although not to the level achieved with megestrol.[33] More recent reports show that oxandrolone, a steroid said to be more anabolic with less androgenic properties will boost appetite, lean body mass and function.[43] Not surprisingly, as illustrated by some of our Olympic and professional athletes, combining exercise with androgen intake strongly enhances muscle size and function. Safer anabolic medications may include oxandrolone and testosterone undecenoate (less risk of hepatic toxicity). In hypogonadal patients, consider testosterone replacement.

Omega-3-fatty acids

The omega-3-fatty acids that we find in dark fatty fish, eg, salmon, tuna, sardines, herring have anti-inflammatory cytokine effects. These may also limit muscle proteolysis.[44] In rodent studies, anti-tumor effects and reduction of chemotherapy toxicity are also commonly reported.[45]

Phase II trials in pancreatic cancer patients and one small randomized trial enrolling patients with various cancers informed us that omega-3s, if taken in doses providing at least 2 grams of eicosapentaenoic acid (EPA) daily had favorable effects on inflammation, appetite and lean body mass. The suggestion of life prolongation has also been made.[46, 47] More recent larger double blind trials in humans did not show a survival effect or demonstrate good appetite stimulation when omega-3 preparations were compared to megestrol.[48] They may, however, sustain or improve lean body mass.

Amino acids

Protein intake should be assured and amino acid mixtures, readily available in the form of whey protein, should be offered to weight losing patients. Do specific amino acid combinations hold particular value? A combination of glutamine, arginine, and β hydroxyl methyl butyrate (the latter a metabolite of leucine) has been studied in small controlled trials in both AIDS and cancer populations.[49,50] Evidence of weight gain and

increase in lean body mass was noted. Comparisons of whey protein with specific amino acid mixtures have not been carried out.

NSAIDs

Eicosanoid production is enhanced in chronic inflammatory states.[51] A specific eicosanoid, 5 hydroxy Eicosa tetranoic acid (15-HETE) may modulate the activity of proteolysis inducing factor (PIF).[51] NSAIDs can reduce tumor growth and tumor wasting in some animal models.[52] Swedish and British work supports the benefits of indomethacin or ibuprofen in reducing cachexia in cancer patients.[53,54] A recent phase III trial in humans comparing megestrol acetate, given with or without ibuprofen, did not show improved appetite or weight gain with the addition of the anti-inflammatory agent.[48] While COX-2 inhibitors are commonly used for pain control in North America, only modest COX-2 laboratory or clinical studies on cachexia are available. [55,56] Clinical trials are awaited.

Multivitamins

The geriatric literature supports the routine use of multivitamin support for institutionalized patients while malnourished cancer patients are at risk for developing unrecognized deficiencies.[57,58] Studies on vitamin use in cachectic patients are not available. Studies on the use of antioxidants in combination with other anticachexia measures are ongoing.[59]

Exercise – rehabilitation

'If you don't use it, you lose it' – muscles require stimulation in order to thrive. Common sense dictates that we encourage muscular activity as long as it is safe. This is backed up by a growing body of evidence that exercise may fundamentally affect cancer incidence and course, the adverse effects of therapy, and fatigue. [60,61,62,63,64,65] Borrowing from geriatric literature, tailored exercise may even benefit fragile patients. As a result, it is reasonable to advise weight losing patients to begin, or maintain, a rehabilitation program if dangerous bone metastases and cardiovascular capacity are taken into account.

Include physiotherapists on the comprehensive cancer care team. They will greatly enhance our ability to include exercise as part of an overall patient prescription for functional assessment and rehabilitation.

Dietary advice

Through simple, easily understood counseling, patients and families can improve the quality and quantity of eating, and take satisfaction in their role as partners in combating wasting. Suggestions to assist patients or family members involved in food preparation follow are included in the Appendix. This general advice can be offered by busy clinicians. Ideally, a dietitian who can tailor a patient specific program and follow up on suggestions should be a member of the comprehensive cancer care team.

Summary

The cancer anorexia/weight loss syndrome remains challenging. Although some aspects of its pathophysiology have recently been clarified, there remains no treatment that improves all aspects of this syndrome. Today, progestational agents and corticosteroids offer the best opportunities for improving appetite. As our understanding of this entity advances, it is hoped that other, more effective interventions will emerge.

Key take-home points

1. Even weight loss of 5% from pre illness weight has an impact on prognosis.
2. Chronic inflammation plays a pathophysiologic role in cachexia.
3. Treat nutrition impact symptoms.
4. Calories alone cannot reverse cachexia.
5. Progestational agents and steroids stimulate appetite.

Pearls

1. TPN/enteral nutrition are incapable of reversing cachexia.
2. Exercise is an important treatment recommendation.
3. Effective treatment of cachexia will require a multipronged approach (appetite stimulation + anabolic agent + exercise).

Pitfalls

1. Calories alone are not enough.
2. Don't wait to intervene until the patient has lost greater than 10% of pre illness weight.
3. Corticosteroids stimulate appetite (no weight gain) but will cause proximal muscle wasting if treatment is prolonged.

Appendix: Dietary advice

Taste and taste changes

Taste changes decrease appetite and the enjoyment of food. A bitter, metallic or sour taste in the mouth is quite common, as are aversions to certain foods. Many foods normally enjoyed are no longer appreciated and the desire to eat diminishes. Sometimes food seems to have no taste which further leads to poor food intake.

People with a change in appetite are particularly sensitive to the way in which food is prepared and offered. Previously tasty food may taste bland or overly bitter. Suggestions which may help:

1. Experiment with various spices and flavoring. It is common for a person's preferences to change during illness. Try using basil, oregano, rosemary, tarragon or mint with meat, fish, chicken or cottage cheese. Garlic and onions may or may not help.
2. Try flavoring foods with lemon, orange or various other fruit juices. Try various kinds of pickles, chutney, relishes which are sweet or sour.
3. Use sugar in your cooking as this can help to eliminate metallic or salty tastes.
4. Add sauces, gravies or broth to food that tends to be dry. Try fruit based sauces using peaches, pears, oranges, plums or pineapple.
5. Marinate meat, chicken or fish in sweet juices, sweet wine, lemon juice, soy sauce, vinaigrettes or pickle juice or a combination of marinades.
6. If you develop a dislike for meat, try alternative high protein foods such as eggs(omelets, frittatas, egg salad), cottage cheese and fruit plate, cheese (cheese melt, pasta with melted cheese, meatless lasagna, quiche, cheese sandwich), legumes such as chick peas, lentils (hearty legume and vegetable soup, chili, casseroles).
7. If milk products taste different, try adding chocolate or strawberry syrup to milk, custard, pudding or ice cream or add a little fruit and make a milkshake.
8. If the taste of water bothers you, try adding a slice of orange or lemon or mix with fruit juice or fruit punch.
9. If the taste of food is too overwhelming try serving foods cold. The hotter the food the stronger the taste.
10. If the smell of drinks bother you, use a straw. Try cold beverages rather than hot.
11. Try water, including sparkling water such a Perrier or soda water, Ginger ale, Sprite, 7UP, tisane or tea to take away a strange taste.
12. Try sucking on a lemon drop or lifesavers (find your favorite flavor). Try to freshen and clean your mouth before and after eating.
13. Cleanse your mouth with soda water, tea or ginger ale. Rinse with a mixture of baking soda and water.

Temperature

14. Foods that are normally enjoyed when they are warm should be presented when they are warm. However, if appetite for warm food is lost, in part because of food odors, try a cold plate such as cold cheeses, cottage cheese, chicken, salmon or egg salad

with fruit and or crackers, various sandwiches, yogurt and fruit, pudding, custard or a homemade milkshake.

Presentation

15. Vary food color and use garnishes (parsley, dill, slice of tomato or orange) to make food attractive. White chicken, potatoes, and cauliflower on a white plate is unappetizing for all of us.
16. Try and eat food in an atmosphere free of food smells.
17. Serve smaller portions of food. Appetite can be lost when presented with an overwhelming amount of food on a plate; one can always have a second helping.

Atmosphere

18. Mealtime is a social occasion. This should not change; it is important to continue to eat with family and friends. Patients should not feel badly if they eat smaller amounts than others. For their part, family and friends should avoid forcing loved ones to eat; this will not help and may indeed cause problems with abdominal distress and nausea.
19. Eat in a calm, relaxed atmosphere.
20. To relax, turn on favorite music.
21. Set the table with a table cloth or placements to make it more attractive.
22. If you are in the custom of consuming alcohol, before or during your meal, try a little wine, sherry or beer to help stimulate your appetite.

Meal preparation

23. The patient who is making meals should prepare some meals in advance of treatment and freeze them. Alternatively one of the many varieties of mostly prepared meals that are available in the grocery stores can be tried.
24. Before treatments begin, stock your cupboard or freezer with foods that are particularly enjoyed.
25. Try protein rich foods such as peanut butter or one of the many nut butters, various nuts (almonds, cashews, walnuts, pecans and peanuts), cheese, eggs, canned tuna, as well as dried and canned fruit and puddings.
26. If meal preparation is a problem, organizations such as ‘Meals on Wheels’ will make meals to be delivered to the home. They are active in many communities.
27. Eat a sandwich and a bowl of soup with a glass of milk or juice. This is a quick and nutritious meal. A traditional hot meal does not need to be eaten every day to get proper nutrition.

28. Remember that a small container of yogurt with a piece of bread or small muffin contains almost the same amount of calories as a shake.

How many meals?

Often, because of delayed stomach emptying, the patient may be hungry but rapidly lose appetite after a few bites. If this common problem is present:

29. Eat small frequent meals 5 – 6 times through the day. Don't force eating, particularly if the patient is nauseated.
30. For a small meal, a nutrient dense snack will help meet nutritional requirements, examples are a small container of yogurt with a small muffin, or an ounce (30 grams) of cheese on 1 piece of bread.
31. Drink beverages or soup after your meals as liquids tend to fill a person up.
32. Make breakfast the largest meal. Appetite tends to decrease as the day progresses. Try to consume more protein rich foods in the morning. For example, if an egg is usually eaten try adding another egg or consider adding a piece of cheese or make a cheese omelet.
33. Take time eating, and pause occasionally during the meal to avoid feeling full too quickly.

Snacks for appetite loss

Smaller nutrient dense meals suitable for eating throughout the day; 3 smaller meals and 3 to 4 snacks:

34. Snacks using milk products are great choices for protein and energy. Choose a variety of these foods each day such as cheese and crackers, toast or bagel with cheese or cream cheese, cheese and various fruits (pears, grapes or apples), yogurt, frozen yogurt, milkshakes, a glass of chocolate milk, hot chocolate made with milk, hot Ovaltine mixed with milk, pudding, custard, tapioca pudding, ice cream, cream soup, sour cream or yogurt vegetable dips.
35. Starch foods (grain products) are good for energy; these include bread, toast with peanut butter or cheese, sandwiches, rolls, buns, muffins, bagels, various crackers, pita, pizza, cookies or cakes made with nuts and fruits, cereals, granola, dessert breads or loaves.
36. Protein foods (meat and slternatives) such as nuts, seeds, hummus, legume dips, milk products, egg dishes such as omelets, quiche, frittata, scrambled eggs, poached, boiled, egg salad, salmon salad, smoked salmon or other fish, tuna salad, chicken salad.

37. Fruit choices provide a source of quick energy, they includes fruit juices, fruit smoothies, dried fruits such as apricot, apples, pineapple, mango, raisins and mix with various nuts and seeds to create your own trail mix, canned or fresh fruit.

Adapted from The Dietary Guide

Swinton N and MacDonald N McGill University 2004

The complete guide is available in both English and French

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The loss of body weight by patients with solid tumors consisted primarily of the loss of muscle mass and body fat. Even in severe wasting, the patients appear to retain significant amounts of body fat. It is the skeletal muscle which is predominantly lost; the visceral life-supporting system is, to a considerable extent, spared. The nonmuscle tissue including the visceral fraction did not change in this study, and actually appeared to increase in size when comparison was made with the normal contrast population. The loss of total body water was slight.

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100 newly detected lung cancer patients were evaluated. 30% had a weight loss of 10% or more from their preillness stable weight. An elevated resting energy expenditure was found in 74% of the patients. Dietary intake was significantly lower in the weight-losing group.

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During infection or inflammation, the expression of cytochrome P450 and its dependent biotransformation pathways are modified. This review covers the loss that occurs in the major mammalian CYP families in response to infection/inflammation and the mediator pathways that are key to this response

[10] Loprinzi CL, LaurieJA, Wieand HS, et al. Prospective evaluation of prognostic variables from patient-completed questionnaires. *J Clin Oncol.* 1994;12:601-607.

In a North Central Cancer Treatment Group study, 1115 patients with colorectal and lung cancer, patients with a loss of appetite had a far poorer prognosis compared to those who maintained their appetite, and this observation persisted even after adjusting for several other prognostic parameters.

[11] Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001;357(9255):539-545. Full Text

This article reviews the links between cancer and inflammation and discusses the implications of these links for cancer prevention and treatment.

[12] Khan S and Tisdale MJ. Catabolism of adipose tissue by a tumor-produced lipid-mobilising factor. *Int J Cancer*. 1999;80:444-447. Full Text

Lipolysis in white adipose tissue during the process of cancer cachexia is mediated by a tumour factor which stimulates cAMP production, possibly through a beta-adrenergic receptor.

[13] Cariuk P, Lorite MJ, Todorov PT et al. Induction of cachexia in mice by a product isolated from the urine of cachectic cancer patients. *Br J Cancer*. 1997;76(5):606-613.

Urine from cancer patients with weight loss showed the presence of an antigen of M(r) 24,000. The antigen was not present in the urine of normal subjects, patients with weight loss from conditions other than cancer or from cancer patients who were weight stable or with low weight loss (1 kg month(-1)). The antigen is capable of producing a syndrome of cachexia in mice.

[14] Hyltander A, Drott C, Korner U et al. Elevated energy expenditure in cancer patients with solid tumors. *Br J Cancer.* 1990;27(1):9-15.

Cancer patients (n = 106) and non-cancer subjects (n = 96) were classified as weight stable (n = 70) or weight-losing (n = 132). Cancer patients had elevated resting energy expenditure (REE) compared with either weight-losing (23.6 [0.4] vs. 20.5 [0.5] kcal/kg per day, P<0.001) or weight-stable controls (22.0 [0.6] vs. 17.9 [0.4], P<0.001). Increased metabolic rate is independent of malnutrition and an elevated adrenergic state may be a likely explanation.

[15] Simons JPF, Schols AMW, Buurman WA and Wouters EFM. Weight loss and low body cell mass in males with lung cancer: relationship with systemic inflammation, acute phase response, resting energy expenditure, and catabolic and anabolic hormones. *Clinical Science.* 1999;97:215-223. Full Text

In 20 male lung cancer patients, pre-stratified by weight loss of >/=10% (n=10) or of <10% (n=10), Compared with the patients with a weight loss of <10%, those with a weight loss of >/=10% were characterized by higher levels of sTNF-R55 (trend towards significance; P=0.06), and lower levels of albumin (27.4 compared with 34.4 mmol/l; P=0.02), testosterone (13.2 compared with 21.5 nmol/l; P=0.01) and IGF-I (119 compared with 184 ng/ml; P=0.004).

[16] Laviano A, Meguid MM, Rossi-Fanelli Filippo. Cancer anorexia : clinical implications, pathogenesis, and therapeutic strategies. *Lancet Oncology.* 2003;4(11):686-694. Full Text

The optimum therapeutic approach to anorectic cancer patients should include changes in dietary habits, achieved via nutritional counselling, and medication therapy, aimed at interfering with cytokine expression or hypothalamic monoaminergic neurotransmission.

[17] Torelli GF, Meguid MM, Moldawer LL, et al. Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. *Am J Physiol.* 1999;277(3 Pt 2);R850-855. Full Text

Administration of anti-TNFα agent in tumor-bearing rodents resulted in an improvement in weight and appetite compared to animals that received vehicle only.

[18] Baracos VE, DeVivo C, Hoyle DH, Goldberg AL. Activation of the ATP-ubiquitin-proteasome pathway in skeletal muscle of cachectic rats bearing hepatoma. *Am J Physiol.* 1995;268(5 Pt 1):E996-1006.

The ubiquitin proteasome pathway accounts for >80% of lean tissue wasting in cancer, as suggested by studies in an animal model.

[19] Llovera M, Garcia-Martinez C, Lopez-Soriano J, et al. Role of TNF receptor 1 in protein turnover during cancer cachexia using gene knockout mice. *Mol Cell Endocrinol*. 1998;142:183-189.

Implantation of Lewis lung carcinoma in gene knockout mice deficient in TNFα demonstrated a different pattern of wasting compared to tumor-implanted wild-type mice that manifested lower rates of protein degradation and less activation of the ubiquitin proteasome system.

[20] Llovera M, Garcia-Martinez C, Lopez-Soriano J, et al. Protein turnover in skeletal muscle of tumor-bearing transgenic mice overexpressing the soluble TNF receptor-1. *Cancer Lett.* 1998;130:19-27.

TNFα led to a doubling of expression of ubiquitin genes in skeletal muscle.

[21] Todorov P, Cariuk P, McDevitt T, Coles B, et al. Characterization of a cancer cachectic factor. *Nature.* 1996;379:739. Full Text

Discovered a 24-kilodalton proteoglycan from a tumor homogenate from the MAC16 tumor line that produces cachexia in vivo by inducing catabolism of skeletal muscle. The 24K material was also present in urine of cachectic cancer patients, but was absent from normal subjects, patients with weight loss due to trauma, and cancer patients with little or no weight loss.

[22] Todorov PT, McDevitt TM, Meyer DJ, Ueyama H, et al. Purification and characterization of a tumor lipid-mobilizing factor. *Cancer Research.* 1998;58:2353.

Cancer patients with weight loss showed urinary excretion of a lipid-mobilizing factor (LMF), determined by the ability to stimulate lipolysis in isolated murine epididymal adipocytes. Such bioactivity was not detectable in the urine of cancer patients without weight loss or in normal subjects.

[23] Hirai K, Hussey HJ, Barber MD, Price SA, Tisdale MJ. Biological evaluation of a lipid-mobilizing factor isolated from the urine of cancer patients. *Cancer Research.* 1998;58:2359.

In a study of 16 patients with cancer, only those with weight loss had detectable concentrations of a lipid-mobilizing factor in their urine

[24] Woods D, Onambele G, Woledge R et al. Angiotensin-I converting enzyme genotype-dependent benefit from hormone replacement therapy in isometric muscle strength and bone mineral density. *J Clin Endocrinology and Metabolism*. 2001;86(5):2200-2204. Full Text

Those taking hormone replacement therapy showed a significant gain in normalized muscle maximum voluntary force slope, the rate of which was strongly influenced by ACE genotype.

[25] Zigman JM and Elmquist JK. Minireview: From anorexia to obesity – the yin and yang of body weight control. *Endocrinolgy*. 2003;144(9):3749-3756. Full Text

In this review, we discuss the mechanisms by which metabolic signals interact with key behavioral, neuroendocrine, and autonomic regulatory regions of the central nervous system. We offer a model in which hormones such as leptin and ghrelin interact with similar central nervous system circuits and

engage them in such a way as to maintain an appropriate and tight regulation of body weight and food intake.

[26] Aleman MR, Santolaria F, Batista N. Leptin role in advanced lung cancer. A mediator of the acute phase response or a marker of the status of nutrition? *Cytokine*. 2002;19(1):21-26. Full Text

76 patients newly diagnosed of non surgical non-small cell lung cancer before chemotherapy treatment and 30 healthy controls were included. Body mass index, serum leptin and cholesterol levels and lymphocyte count were decreased in lung cancer patients. Cytokine IL-6, TNF-alpha, sTNF-RII, sIL-2R, IL-12, IL-10 and IFN-gamma, and other acute phase reactants as alpha1 antitrypsin, ferritin, CRP and platelets were all raised in patients, whereas the IL-2 was decreased. Circulating leptin concentrations are not elevated in weight-losing cancer patients and are inversely related to the intensity of the inflammatory response.

[27] Shimizu Y, Nagaya N, Isobe T et al. Increased plasma ghrelin level in lung cancer cachexia. *Clinical Cancer Research*. 2003;9:774-778. Full Text

Plasma ghrelin level did not significantly differ between 43 patients with lung cancer and controls (157 +/- 10 versus 132 +/- 8 fmol/ml, P = 0.1). However, plasma ghrelin level was significantly higher in patients with cachexia than in those without cachexia (180 +/- 17 versus 135 +/- 10 fmol/ml, P = 0.011). Increased ghrelin may represent a compensatory mechanism under catabolic-anabolic imbalance.

[28] Slaviero KA, Clarke SJ, Rivory LP. Inflammatory response: an unrecognized source of variability in the pharmacokinetics and pharmacodynamics of cancer chemotherapy. *Lancet Oncology*. 2003;4(4):224-233.

[29] Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer*. 2000;88(9):2164:2171.

[30] EORTC quality of life questionnaire (QLQ C-30). Available at http://www.eortc.be/home/qol/ExplQLQ-C30.htm. Accessed March 26, 2005.

[31] Kaasa T, Loomis J, Gillis K, Bruera E, Hanson J. The Edmonton Functional Assessment Tool: Preliminary development and evaluation for use in palliative care. *Journal of Pain & Symptom Management*. 1997;13(1):10-19.

[32] Anonymous. Parenteral nutrition in patients receiving cancer chemotherapy. *Annals of Internal Medicine*. 1989;110(9):734-736.

A commentary on the use of parenteral nutrition in patients with cancer.

[33] Ovesen L, Allingstrup L, Hannibal J, Mortenson EL, Hansen OP. Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. *Journal of Clinical Oncology.* 1993;11:2043-2049.

Randomly assigned105 cancer patients who were receiving chemotherapy to nutritional counseling versus no such counseling. Patients who received the counseling ate more, but this increased caloric intake led to no significant weight gain, no significant improvement in quality of life, no improvement in tumor response rate to chemotherapy, and no survival advantage within the group that received the counseling.

[34] Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol.* 1999;17:3299-3306. Full Text

Fluoxymesterone resulted in significantly less appetite enhancement and did not have a favorable toxicity profile. Megestrol acetate and dexamethasone caused a similar degree of appetite enhancement and

similar changes in nonfluid weight status, with nonsignificant trends favoring megestrol acetate for both of these parameters. Dexamethasone was observed to have more corticosteroid-type toxicity and a higher rate of medication discontinuation because of toxicity and/or patient refusal than megestrol acetate (36% v 25%; P =.03).

[35] Loprinzi CL, Ellison NM, Schaid DJ, Krook JE, Athmann LM, Dose AM. Mailliard JA, Johnson PS, Ebbert LP. Geeraerts LH. Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. *Journal of the National Cancer Institute*. 1990;82:1127-1132.

133 cancer patients with the cancer anorexia/weight loss syndrome in a North Central Cancer Treatment Group trial. Patients who received megestrol acetate at a dose of 800 mg/day reported an improved appetite and an increase in non-fluid weight.

[36] Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer*. 1974;33:1607-1609. PMID: 4135151.

[37] Loprinzi CL, Bernath AM, Schaid DJ, et al. Phase III evaluation of 4 doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *J Clin Oncol.* 1993;11:762-767.

A direct dose-response endpoint found that doses from 480 to 800 mg/day are better than 160 mg/day. The higher dose of 1280 mg/day was not any more effective.

[38] Personal Communication

[39] Lambert CP, Sullivan DH, Freeling SA et al. Effects of testosterone replacement and/or resistance exercise on the composition of megestrol acetate stimulated weight gain in elderly men: A randomized controlled trial. *J Clin Endocrinology and Metabolism.* 2002;87(5):2100-2106. Full Text

Thirty older men (aged 67.0 +/- 5.8) completed this 12-wk study. All subjects received megestrol acetate and were randomly assigned to a treatment group. The mean increase in body weight for all groups was not different between groups. Despite significant weight gain, megestrol acetate appears to have an antianabolic effect on muscle size even when combined with testosterone replacement. Resistance exercise attenuated this reduction in muscle mass and when combined with T had an anabolic effect on muscle mass.

[40] Loprinzi CL, Fonseca R, Jensen MD. Megestrol acetate-induced adrenal suppression [letter]. *Journal of Clinical Oncology.* 1996;14:689. PMID: 8636799.

[41] Harrold JA and Williams G. The cannabinoid system: a role in both the homeostatic and hedonic control of eating? *British Journal of Nutrition*. 2003;90:729-734. Full Text

Cannabinoid system activity in the hypothalamus is thought to contribute to the homeostatic regulation of energy balance, under the control of the hormone leptin. A second component of cannabinoid-mediated food intake appears to involve reward pathways and the hedonic aspect of eating.

[42] Sakamoto M, Mikasa K, Toshimasa M et al. Anti-cachectic effect of clarithromycin for patients with unresectable non-small cell lung cancer. *Chemotherapy*. 2001;47:444-451. Full Text

Clarithromycin was administered to 33 patients with unresectable primary non-small cell lung cancer, who had received chemotherapy, radiotherapy or both (basic cancer therapy). After 3 months of clarithromycin treatment, serum levels of IL-6 significantly decreased and body weight increased.

[43] Von Roenn JH, Tchekmedyian S, Hoffman R et al. Safety of oxandrolone in cancer-related weight loss. ASCO Poster #3013. 2003.

[44] Calder PC. More good news about fish oil. *Nutrition*. 2001;17:158-160. Full Text

[45] Tisdale MJ. Protein loss in cancer cachexia. *Science*. 2000;289:2293-2294. PMID: 11041796. Full Text

[46] Hardman WE, Moyer MP, Cameron IL. Consumption of an omega-3 fatty acids product, INCELL AAFA reduced side-effects of CPT-11 (ironotecan) in mice. *Br J Cancer.* 2002;86:983-988. Full Text

2% omega-3 polyunsaturated fatty acid product containing a high concentration of long chain fatty acids in the diet reduced the side effects of CPT-11 treatment in mice.

[47] Gogos CA, Ginopoulos P, Salsa B et al. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy : a randomized control trial. *Cancer.* 1998;82:395-402. Full Text

Sixty patients with generalized solid tumors were randomized to receive dietary supplementation with either fish oil (18 g of omega-3 polyunsaturated fatty acids, PUFA) or placebo daily until death. Each group included 15 well-nourished and 15 malnourished patients. Omega-3 polyunsaturated fatty acids had a significant immunomodulating effect and seemed to prolong the survival of malnourished patients with generalized malignancy.

[48] Jatoi A, Rowland KH Jr, Loprinzi Cl, et al. A Phase III, double blind, placebo controlled randomized comparison of megestrol acetate (megace) versus nan omega-3 fatty acid (EPA-enriched nutritional supplement versus both). Abstract ASCO 2003.

[49] Fearon KCH, von Meyenfeldt MF, Moses AGW et al. Effect of a protein and energy dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut.* 2003;52:1479-1486. Full Text

A total of 200 patients were randomised to consume two cans/day of the experimental (n-3 fatty acids, especially eicosapentaenoic acid), or control supplement for eight weeks in a multicentre, randomised, double blind trial. Patients in both groups stopped losing weight. Intention to treat group comparisons indicated that at the mean dose taken, enrichment with n-3 fatty acids did not provide a therapeutic advantage.

[50] Clark RH, Feleke G, Mehraj D et al. Nutritional treatment for acquired immunodeficiency virus-associated wasting using β-hydroxy β-methylbutyrate, glutamine, and arginine: A randomized, double-blind, placebo-controlled study. *Journal of Parenteral and Enteral Nutrition.* 2000;24(3):133-139.

Sixty-eight human immunodeficiency virus (HIV)-infected patients with a documented weight loss of at least 5% in the previous 3 months were randomly assigned in a double-blind fashion to receive either placebo containing maltodextrin or a nutrient mixture containing 3 g HMB, 14 g L-glutamine, and 14 g L-arginine given in two divided doses daily for 8 weeks. Forty-three subjects completed the 8-week protocol, (placebo, n = 21; HMB/Arg/Gln, n = 22). At 8 weeks, the subjects consuming the HMB/Arg/Gln mixture gained 3.0 +/- 0.5 kg of BW while those supplemented with the placebo gained 0.37 +/- 0.84 kg (p = .009).

[51] Ross JA and Fearon KCH. Eicosanoid-dependent cancer cachexia and wasting. *Curr Opin Clin Nutr Metab Care.* 2002;5(3):241-248. Full Text

This review examines the biology of the eicosanoids and the evidence of a role for the eicosanoids in cancer cachexia and wasting.

[52] Lonroth C, Svaninger G, Gelin J et al. Effects related to indomethacin prolonged survival and decreased tumor growth in a mouse tumor model with cytokine dependent cancer cachexia. *Int J Oncol.* 1995;7:1405-1413.

[53] Wigmore SJ, Barber MD, Ross JA, et al. Effect of oral eicosapentaenoic acid on weight loss inpatients with pancreatic cancer. *Nutr cancer*. 2000;36:177-184.

Twenty-six patients with advanced pancreatic cancer were entered into the study. Eicosapentanenoic aced (95% pure) was administered at 1 g/day; the dose was increased o 6 g/day over four weeks, and then a maintenance dose of 6 g/day was administered. After four weeks of supplementation, patients had a median weight gain of 0.5 kg (p=0.0009 vs. rate of weight loss at baseline), and this stabilization of weight persisted over the 12-week study period.

[54] McMillan DC, Wigmore SJ, Fearon KCH et al. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. *Br J Cancer.* 1999;79:495-500. Full Text

38 and 35 patients (median weight loss 18%) were randomized to megestrol acetate/placebo or megestrol acetate/ibuprofen, respectively, for 12 weeks. Forty-six (63%) of patients failed to complete the 12-week assessment. Of those evaluable at 12 weeks, there was a decrease in weight (median 2.8 kg) in the megestrol acetate/placebo group compared with an increase (median 2.3 kg) in the megestrol acetate/ibuprofen group (P<0.001).

[55] Davis TW, Zweifel BS, O'Neal JM et al. Inhibition of cyclooxygenase-2 by celexicob reverses tumor-induced wasting. *Pharmacology and Experimental Therapeutics.* 2004;308(3):929-934. Full Text

Despite the observation that no significant impact on tumor growth was observed between vehicle and celecoxib-treated animals over the course of the mouse studies, celecoxib rapidly reversed weight loss.

[56] Lunholm K, Daneryd P, Korner U, et al. Evidence that long term COX-treatment improves energy homeostasis and body composition in cancer patients with progressive cachexia. *Int J Oncol*. 2004;24:505-512.

A retrospective case control analysis was performed. Weight-losing untreated cancer patients had elevated resting energy expenditure compared to undernourished non-cancer patients (23.3+-/-0.1,m=702 vs 20.9+/-0.3 kcal/kg/day, n=132, p<0.001). This difference became significantly reduced by long-term indomethacin treatement (p<0.003).

[57] Girodin F, Galan P, Monget AL et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients. *Arch Intern Med.* 1999;159:748-754. Full Text

This randomized, double-blind, placebo-controlled intervention study included 725 institutionalized elderly patients (>65 years) from 25 geriatric centers in France. Patients received an oral daily supplement of nutritional doses of trace elements (zinc and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) or a placebo within a 2 x 2 factorial design for 2 years. The number of patients without respiratory tract infections during the study was higher in groups that received trace elements (P = .06).

[58] Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention. *JAMA.* 2002;287(23):3117-3125. Full Text

Some groups of patients are at higher risk for vitamin deficiency and suboptimal vitamin status. Inadequate intake of several vitamins has been linked to chronic diseases, including coronary heart disease, cancer, and osteoporosis.

[59] Mantovani G, Maccio A, Madeddu C et al. Antioxidant agents are effective in inducing lymphocyte progression through cell cycle in advanced cancer patients: assessment of the most important laboratory indexes of cachexia and oxidative stress. *J Mol Med.* 2003;81(10):664-673. Full Text

The percentage of phytohemaglutinin-stimulated peripheral blood mononuclear leukocytes of cancer patients entering S phase, which was significantly lower than that of controls, increased significantly to more than physiological level after coculture with antioxidants. Serum levels of IL-1 beta, IL-6, and

TNFalpha were significantly higher and serum levels of IL-2 and leptin significantly lower in cancer patients than controls. Serum levels of C-reactive protein and fibrinogen were significantly higher in cancer patients than controls. Patients with advanced cancer thus exhibit both a high-grade oxidative stress and a chronic inflammatory condition

[60] Thune I, Brenn T, Lund E et al. Physical activity and the risk of breast cancer. *N Engl J Med.* 1997;336:1269-1275. Full Text

During a median follow-up of 13.7 years, we identified 351 cases of invasive breast cancer among the 25,624 women in the cohort. Greater leisure-time activity was associated with a reduced risk of breast cancer. (relative risk, 0.63; 95 percent confidence interval, 0.42 to 0.95) among women who exercised regularly, as compared with sedentary women (P for trend=0.04).

[61] Segal RJ, Reid RD, Courneya KS. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol.* 2003;21(9):1651-1652. Full Text

Men assigned to resistance exercise had less interference from fatigue on activities of daily living (P =.002) and higher quality of life (P =.001) than men in the control group.

[62] Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol.* 2005;23:899-909.

26 studies were reviewed. The majority demonstrate physiological and psychological benefits. Most studies have involved breast cancer patients. Recent evidence supports resistance exercise (e.g. weight training) over cardiovascular exercise (eg walking) to counteract some side effects of cancer management and improve physical function and quality of life.

[63] Courneya KS, Mackey JR, Bell GJ et al. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J Clin Oncol.* 2003;21(9):1651-1652. Full Text

Fifty-two participants completed the trial. Overall QOL increased by 9.1 points in the exercise group compared with 0.3 points in the control group (mean difference, 8.8 points; 95% CI, 3.6 to 14.0; P =.001).

[64] Lucia A, Earnest C, Perez M. Cancer-related fatigue: can exercise physiology assist oncologists? *Lancet Oncology.* 2003;4(10):616-625. Full Text

Advising fatigued cancer patients to rest paradoxically compound symptoms of fatigue, since sedentary habits induce muscle catabolism and thus cause a further decrease in functional capacity. By contrast, there is scientific evidence that an exercise programme of low to moderate intensity can substantially reduce cancer-related fatigue and improve the quality of life of these patients.

[65] Binder Ef, Schechtman KB, Ehsani AA, et al. Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. *JAGS.* 2002;50:1921-1928.

In 115 sedentary men and women (mean age 83) with mild to moderate physical frailty exercise therapy resulted in significantly greater improvements than control home exercise.