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**Title:** Current treatment options for colon cancer peritoneal carcinomatosis

**Running title:** Update in colon cancer peritoneal carcinomatosis

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**Abstract**

Peritoneal carcinomatosis (PC), the dissemination of cancer cells throughout the lining of the abdominal cavity, is the second most common presentation of colon cancer distant metastasis. Despite remarkable advances in cytotoxic chemotherapy and targeted therapy for colon cancer over the last 15 years, it has been repeatedly shown that these therapies remain ineffective for colon cancer PC. Recently, there has been a rapid accumulation of reports that cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) prolongs the life of colon cancer PC patients. Here, we will review the clinical presentation, the mechanisms of disease progression, and current treatment options for colon cancer PC, with a focus on the benefits and limitations of CRS-HIPEC.

**Key words:** Cancer; Colorectal; Carcinomatosis; Peritoneal; hyperthermic intraperitoneal chemotherapy; Intraperitoneal chemotherapy; Cytoreductive surgery; Mechanism

**Core tip:** This review aims to present the clinical presentation, the mechanisms of disease progression, and current treatment options for colon cancer peritoneal carcinomatosis, with a focus on the benefits and limitations of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy.

**Abstract**

It is estimated that half of all patients with cancer eventually develop a syndrome of cachexia, with anorexia and a progressive loss of adipose tissue and skeletal muscle mass. Cancer cachexia is characterized by systemic inflammation, negative protein and energy balance, and an involuntary loss of lean body mass. It is an insidious syndrome that not only has a dramatic impact on patient quality of life, but also is associated with poor responses to chemotherapy and decreased survival. Cachexia is still largely an underestimated and untreated condition, despite the fact that multiple mechanisms are reported to be involved in its development, with a number of cytokines postulated to play a role in the etiology of the persistent catabolic state. Existing therapies for cachexia, including orexigenic appetite stimulants, focus on palliation of symptoms and reduction of the distress of patients and families rather than prolongation of life. Recent therapies for the cachectic syndrome involve a multidisciplinary approach. Combination therapy with diet modification and/or exercise has been added to novel pharmaceutical agents, such as Megestrol acetate, medroxyprogesterone, ghrelin, omega-3-fatty acid among others. These agents are reported to have improved survival rates as well as quality of life. In this review, we will discuss the emerging understanding of the mechanisms of cancer cachexia, the current treatment options including multidisciplinary combination therapies, as well an update on new and ongoing clinical trials.

**Key words:** cancer cachexia, Pharmacological Treatment, Physical Exercise

**Introduction**

Although there is no single universally agreed upon definition of cachexia, a recent consensus statement states that cachexia is a complex metabolic syndrome associated with underlying illness, and is characterized by the loss of muscle with or without loss of fat mass. Cachexia is seen in many medical conditions, including cancer, acquired immunodeficiency syndrome (AIDS), chronic obstructive pulmonary disease, multiple sclerosis, chronic heart failure, tuberculosis, familial amyloid polyneuropathy, mercury poisoning (acrodynia) and hormonal deficiency [[1](#_ENREF_1), [2](#_ENREF_2)]. Cancer cachexia is characterized by systemic inflammation, negative protein and energy balance, and an involuntary loss of lean body mass, with or without wasting of adipose tissue [[3](#_ENREF_3)]. Clinically, cachexia is represented by significant weight loss in adults and failure to thrive in children [[4](#_ENREF_4)], accompanied by alterations in body composition and a disturbed balance of biological systems [[5-7](#_ENREF_5)]. Whilst the loss of skeletal muscle mass is the most obvious symptom of cancer cachexia, cardiac muscle is also depleted, though muscle of other visceral organs tend to be preserved. Though cachexia is seen in several disease states, the loss of muscle mass has been shown to occur most rapidly in cancer patients [[8](#_ENREF_8)].

Cancer cachexia is an insidious syndrome that not only has a dramatic impact on patient quality of life, but is also associated with poor responses to chemotherapy and survival [[9-11](#_ENREF_9)]. Indeed, cachexia occurs in the majority of terminal cancer patients and, according to Warren, is responsible for the death of 22% of cancer patients [[12](#_ENREF_12), [13](#_ENREF_13)].

Current therapies focus on palliation of symptoms and the reduction of distress of patients and families rather than cure [[14](#_ENREF_14)]. In many cases, cachexia remains a largely underestimated and untreated condition [[4](#_ENREF_4), [15](#_ENREF_15)]. Approximately half of all patients with cancer experience cachexia [[16](#_ENREF_16), [17](#_ENREF_17)], with the prevalence rising as high as 86 % in the last 1–2 weeks of life [[18](#_ENREF_18), [19](#_ENREF_19)], and with 45 % of patients lose more than 10 % of their original body weight over the course of their disease progression [[19](#_ENREF_19)]. Death usually occurs when there is 30 % weight loss [[5](#_ENREF_5)]. The best management strategy of cancer cachexia is to treat the underlying cancer as this will completely reverse the cachexia syndrome. Unfortunately, this remains an infrequent achievement with advanced cancers. A second option could be to counteract weight loss by increasing nutritional intake, but since in the majority of cachectic patients anorexia is only a part of the problem, nutrition as a unimodal therapy has not been able to completely reverse the wasting associated with cachexia.

In this review, we discuss the presentation, mechanisms, and current treatment options for cancer cachexia, including diet and exercise therapy to improve quality of life as well as prognosis for affected patients.

**Cancer cachexia and malignant inflammation**

Multiple mechanisms are involved in the development of cachexia, including anorexia, decreased physical activity, decreased secretion of host anabolic hormones, and an altered host metabolic response with abnormalities in protein, lipid, and carbohydrate metabolism [[20](#_ENREF_20)]. Due to the complex clinical findings, guidelines for the diagnosis of cachexia have just recently started to appear [[3](#_ENREF_3)]. Even so, there is great variation in definitions, which presents problems when comparing studies and informing clinical diagnoses [[21](#_ENREF_21), [22](#_ENREF_22)].

One proposed mechanism of cancer cachexia is that it is an integrated physiological response of substrate mobilization driven by inflammation [[23](#_ENREF_23)].　There is an increase in pro-inflammatory cytokine activity during cancer progression [[24](#_ENREF_24), [25](#_ENREF_25)], and systemic inflammation is a hallmark of cancer cachexia, indicated by the production of acute-phase response (APR) proteins such as C-reactive protein (CRP) and fibrinogen [[26](#_ENREF_26), [27](#_ENREF_27)]. CRP is considered to be an accurate measure of the pro-inflammatory cytokine activity [[28](#_ENREF_28)] that has been implicated in muscle wasting [[29](#_ENREF_29)]. The APR is related to the inflammation and weight loss seen in cachexia [[30](#_ENREF_30), [31](#_ENREF_31)] and the reduced quality of life and shortened survival of cachexia patients [[10](#_ENREF_10), [32-35](#_ENREF_32)]. These phenomena increase muscle catabolism and transfer amino acids from muscle anabolism toward the amino acid pool required for APR protein anabolism [[36](#_ENREF_36), [37](#_ENREF_37)]. It has been suggested that eicosanoids also mediate inflammation in cancer cachexia [[38-40](#_ENREF_38)].

There is considerable evidence that signaling through cytokines and myostatin/activin pathways has a role in cancer cachexia and anorexia [[41-43](#_ENREF_41)]. Numerous cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-gamma (IFN-γ), have been postulated to play a role in the etiology of cancer cachexia [[44-52](#_ENREF_44)]. The cytokines are transported across the blood-brain barrier where they interact with the luminal surface of brain endothelial cells causing release of substances that affect appetite [[53](#_ENREF_53)]. Receptors of TNF-α and IL-1 are found in the hypothalamic areas of the brain, which regulates food intake. Anorexia induced by both TNF-α and IL-6 can be blocked by inhibitors of cyclooxygenase, suggesting that a prostaglandin (PG), such as PGE2, may be the direct mediator of appetite suppression [[54](#_ENREF_54)].

The role of TNF-α in mediating cancer cachexia is supported by evidence that intraperitoneal injection of a soluble recombinant human TNF-receptor antagonist improved food take and weight gain in tumor-bearing rats [[55](#_ENREF_55)]. TNF-α increases gluconeogenesis, lipolysis and proteolysis, decreases the synthesis of proteins, lipids and glycogen, induces the formation of IL-1 [[17](#_ENREF_17)], and stimulates the expression of Uncoupling proteins (UCP) 2 and UCP3 in cachectic skeletal muscle [[8](#_ENREF_8)]. Despite the fact that TNF-α induces the symptoms of cachexia, its inhibition has not been shown to stop or to reverse cancer cachexia [[49](#_ENREF_49)]. This indicates that though TNF-α may be involved in the development of cachexia, it is not solely responsible for the effects seen in cachectic patients.

IL-1 concentrations increase in the cachectic state and have been known to cause similar effects to TNF-α [[56](#_ENREF_56)]. IL-1 induces anorexia in cachectic patients as it causes an increase in plasma concentrations of tryptophan, which in turn increases serotonin levels, causing early satiety and suppressing hunger [[57](#_ENREF_57)]. Increased tryptophan leading to associated increased serotonin production from the hypothalamus has been linked to anorexia [[57](#_ENREF_57), [58](#_ENREF_58)]. A conflicting study showed that IL-1 did not affect food intake or weight loss, suggesting that IL-1 has a local effect on a particular tissue or the exogenous doses of IL-1 must be larger in order to see characteristics of cachectic state [[59](#_ENREF_59)].

IL-6 is an important mediator in the defense mechanism of humans through its regulation of immune responses [[60](#_ENREF_60)]. Concentration levels of IL-6 increase transferrin in cancer patients [[28](#_ENREF_28)]. Levels of IL-6 were observed to be higher in patients with cachexia than weight-stable patients. Although IL-6 may have an important role in the development of cachexia, it is not considered to be solely responsible, working through indirect action, indicated by the failure of IL-6 administration to reproduce cachexia in animal model [[17](#_ENREF_17)]. As such, it is likely that a complex interplay of these factors is responsible for cachexia, rather than each working in isolation [[61](#_ENREF_61)]. However, since there is limited variation in levels of circulating cytokines [[62](#_ENREF_62)], and circulating cytokines are produced by isolated peripheral mononuclear cells, it is speculated that local production in affected tissues is more important and relevant to cachexia than systemic circulation of these factor [[63](#_ENREF_63)].

Signal Transducers and Activators of Transcription 3 (STAT3) is a member of the STAT family of proteins. STAT3 function as essential signal transducing effector proteins of cytokine-induced pathways that control the development, proliferation, differentiation, homeostasis of many cell types [[64](#_ENREF_64)]. STAT3 activation is a common feature of muscle wasting. STAT3 is activated in muscle by IL-6 and by different types of cancer and sterile sepsis [[65](#_ENREF_65)]. It is not certain whether the cytokine production is primarily from tumor or host inflammatory cells. It has been hypothesized that either tumor cell production of pro-inflammatory cytokines or the host inflammatory cell response to tumor cells is the source of the APR protein seen in many malignancies and in cachexia [[66](#_ENREF_66)] .

**Catabolism**

A number of factors in cancer patients are known to increase the catabolic response, leading to unsustainable levels of fat and muscle mobilization and levels of muscle depletion that cause significant morbidity and mortality.

The metabolic changes found in cachexia resemble those of infection rather than starvation and are multifactorial and complex [[67](#_ENREF_67)]. Although the weight loss brought on by starvation is mainly from adipose tissue stores, the weight loss of cancer cachexia is caused by loss of both skeletal muscle and adipose tissue mass [[68](#_ENREF_68)]. In patients with cachexia there is an increase in muscle protein catabolism leading to a net loss of muscle mass. This imbalance of protein synthesis and degradation is one of the most obvious aspects of metabolism disruption in cancer cachexia. It has been widely observed that the rate of muscle protein catabolism increases in cachexia, whilst anabolism of new proteins decreases, resulting in net protein breakdown [[8](#_ENREF_8), [69-71](#_ENREF_69)].

Increased energy expenditure may also contribute to the wasting process. Resting energy expenditure (REE) is increased in the cachectic state, with futile metabolic cycling accounting for much of this increase [[72](#_ENREF_72)]. About 70% of the total energy expenditure in sedentary people arises from the REE [[1](#_ENREF_1)]. The REE in cancer patients is strongly determined by the type of tumor. For example, patients with pancreatic and lung cancer had increased REE compared with healthy subjects　[[73](#_ENREF_73), [74](#_ENREF_74)]. Patients with gastric and colorectal cancer were reported to have no elevation of REE [[73](#_ENREF_73)], though it seems that these results reflect how close the patients were to death at the time of measurement. In malnourished patients near death there is an increase in REE and in protein catabolism which could relate to the utilization of the last skeletal muscle mass [[75](#_ENREF_75)].

Although skeletal muscle is the most important site for thermogenesis in the adult human, brown adipose tissue (BAT) is also to have an important role in cachexia. Non-shivering thermogenesis takes place in BAT, and in a single study using autopsy samples of peri-adrenal tissue examined by light microscopy, BAT was observed in 20 of the cachectic cancer patients (80%) compared to 2 of the age-matched subjects (13%) [[76](#_ENREF_76)].

Uncoupling proteins (UCPs), related to the regulation of mitochondrial proton gradients and the production of reactive oxygen species (ROS) in skeletal muscle and adipose tissue, may also play a role in the increased REE observed in cachexia [[8](#_ENREF_8)]. There are three UCPs: UCP1 found only in BAT, UCP2 found in most tissues, and UCP3 found only in BAT and skeletal muscle [[77](#_ENREF_77)]. In particular, the expression of UCP2 and UCP3, associated with energy expenditure and metabolism in skeletal muscle, is upregulated in the cachectic state, indicating involvement of these mechanisms [[8](#_ENREF_8)]. Expression levels of mRNA of UCP1 in BAT were significantly elevated over controls in mice bearing cachexia inducing tumors, while expression levels of UCP2 and -3 did not change in BAT, but were significantly increased in skeletal muscle [[78](#_ENREF_78)]. This may also be applicable to cancer patients, since UCP-3 mRNA levels are increased in muscle only when weight loss is associated with cancer. UCP-2 mRNA levels in muscle seems unaffected by cancer either with or without weight loss [[79](#_ENREF_79)]. The increase in UCP3 mRNA might enhance energy expenditure and contribute to tissue catabolism.

**Pharmacological Treatment**

**MEGACE**

Megestrol acetate (MEGACE) and medroxyprogesterone (MPA) are synthetic, orally active derivatives of the naturally occurring hormone, progesterone.

MEGACE was first synthesized in England in 1963. Developed as an oral contraceptive, the agent was first tested in the treatment of breast cancer in 1967 and, was later tested for the treatment of endometrial cancer. MEGACE is currently used to improve appetite and to increase weight in cancer-associated anorexia. From September 1993, MEGACE was approved by the Food and Drug Administration (FDA) in the USA for the treatment of anorexia, cachexia or unexplained weight loss in patients with AIDS. MEGACE has been found to improve appetite, caloric intake and nutritional status in several clinical trials [[80-90](#_ENREF_80)]. Recently a meta-analysis of 35 trials, comprising 3963 patients, for the effectiveness of MEGACE was conducted [[91](#_ENREF_91)], demonstrating a beneﬁt of MEGACE compared with placebo, particularly with regard to appetite improvement and weight gain in cancer. Higher doses were more related to weight improvement than lower doses. Quality of life improvement in patients was seen only when comparing MEGACE versus placebo [[91](#_ENREF_91)]. The mechanism for the associated weight gain is mostly unknown, although MEGACE may stimulate the synthesis, transport, and release of neuropeptide Y, known to produce appetite-stimulating effects in rats [[92](#_ENREF_92)].

MPA has similarly been shown to increase appetite and food intake with a stabilization of body weight [[93](#_ENREF_93)]. There is evidence that high-dose synthetic progestins have effects on both appetite and body weight, the two clinical hallmarks most widely identified in patients with cancer anorexia and cachexia [[94](#_ENREF_94)]. MPA has been shown to reduce the in vitro production of serotonin and cytokines (IL-1, IL-6 and TNF-α) by peripheral blood mononuclear cells of cancer patients [[92](#_ENREF_92), [93](#_ENREF_93), [95](#_ENREF_95), [96](#_ENREF_96)]. These findings have also been replicated in the clinical setting, with IL-1, IL-6, and TNF- α levels in serum reported to be decreased in cancer patients after MEGACE or MPA treatment [[93](#_ENREF_93)].

**Ghrelin**

Ghrelin, a 28-amino-acid gastric peptide hormone, was first identified in the rat stomach in 1999 as an endogenous ligand for the growth hormone secretagogue receptor [[97](#_ENREF_97)]. The functions of ghrelin in­clude food intake regulation, gastrointestinal (GI) motility, and acid secretion in the GI tract. Many GI disorders involving infection, inflammation, and malignancy are correlated with altered ghrelin production and secretion [[98](#_ENREF_98)]. Circulating levels of ghrelin are noted to be increased when human melanoma cells are implanted in nude mice [[99](#_ENREF_99)]. In a similar manner, circulating levels of both acyl and des-acyl ghrelin are elevated in cachectic cancer patients with gastric cancer [[100](#_ENREF_100), [101](#_ENREF_101)] and lung cancer [[102](#_ENREF_102), [103](#_ENREF_103)]. The levels of acyl-ghrelin are reported to be 50% higher in cancer patients with cachexia [[104](#_ENREF_104)]. These elevated levels of ghrelin could represent a counter regulatory mechanism to fight anorexia associated with tumor growth, representing an endocrine response to the so-called ‘ghrelin resistance’ found in cancer patients. This is the rationale behind the clinical studies of high dose ghrelin as a treatment to counteract anorexia in cancer.

An experimental study showed that repeated administration of ghrelin improves cardiac structure and function and attenuates the development of cardiac cachexia in chronic heart failure, with ghrelin thought to regulate energy metabolism through growth hormone dependent and growth hormone independent mechanisms [[105](#_ENREF_105)]. For cancer cachexia, a phase II randomized, placebo-controlled, double-blind study, using an oral ghrelin mimetic was conducted [[105](#_ENREF_105)]. This study demonstrated an improvement in lean body mass, total body mass and hand grip strength in cachectic cancer patients [[105](#_ENREF_105)].

**Cannabinoids**

Cannabinoids, which are present in marijuana, are a class of diverse chemical compounds that activate cannabinoid receptors on cells that repress neurotransmitter release in the brain. Cannabinoids have a definite effect on weight gain and, bearing this in mind, have been used to increase food intake in cancer patients. The main effective constituent of cannabis is delta-9-tetrahydrocannabinol [[106](#_ENREF_106), [107](#_ENREF_107)], but the mechanism by which cannabinoids exert their effects has yet to be clarified. It has been postulated that they may act via endorphin receptors, through inhibition of prostaglandin synthesis [[108](#_ENREF_108)], or by inhibiting IL-1 secretion [[85](#_ENREF_85)]. Despite high expectations for cannabinoids to be effective against cancer-related anorexia/cachexia syndrome, both of the two separate randomized clinical trials carried out by Jatoi et al. [[109](#_ENREF_109)] and Strasser et al. [[110](#_ENREF_110)] have failed to show benefit as compared to MEGACE or placebo, respectively.

**Melanocortin antagonists**

The melanocortin-4 (MC4) receptor subtype plays a pivotal role in body weight regulation [[111](#_ENREF_111)]. Acute and chronic stimulation of MC4 receptors produces anorexia, weight loss, and an increase in metabolic rate, the cardinal features of disease-associated cachexia. Knock-out or antagonism of MC4 receptors in animal models of cachexia protects from anorexia and the loss of both lean and fat body mass, and it is suggested that an MC4 antagonist may be beneficial in wasting diseases, which are poorly treated by available therapies [[112](#_ENREF_112)]. The MC4 receptor is involved in the anorexigenic cascade leading to a decrease in neuropeptide Y and, therefore, a decrease in food intake. The use of MC4 antagonists has been proven to be effective in preventing anorexia associated with cachexia, loss of lean body mass and basal energy in animal models [[112](#_ENREF_112), [113](#_ENREF_113)]; however, there is no clinical data at this time. Future clinical trials are needed to prove the efficacy of this antagonist in the treatment of human cachexia

**Thalidomide and Etanercept**

TNF-α, IL-6, and IFN-c have all been implicated in the pathogenesis of cachexia, and in cachectic tumor bearing murine models treatment with anti-TNF-α, anti-IL-6, and anti-IFN-c antibodies can attenuate the disease process, although it cannot stop or reverse cancer cachexia [[49](#_ENREF_49), [114-120](#_ENREF_114)]. There is also some evidence that cytokines play a role in the pathogenesis of cachexia [[121](#_ENREF_121)]. It has been suggested that by mimicking the hypothalamic effect of excessive negative feedback signaling from leptin by persistent stimulation of anorexigenic peptides, or by inhibition of the neuropeptide Y pathway, cytokines could induce anorexia [[122](#_ENREF_122)]. Thus modulating cytokine expression in cancer patients may also affect cancer associated anorexia. Therapeutic strategies have been based on either blocking cytokine synthesis or their action [[123](#_ENREF_123)].

Thalidomide (a-N-phthalimidoglutaramide) has complex immune-modulatory and anti-inflammatory properties. It has been shown to down-regulate the production of TNF-α and other pro-inflammatory cytokines in monocytes, to inhibit the transcription factor nuclear factor kappa B (NFkB), down-regulate cyclooxygenase 2, and to inhibit angiogenesis [[124](#_ENREF_124), [125](#_ENREF_125)]. One randomized placebo-controlled trial in patients with cancer cachexia showed that the drug was well-tolerated and effective at attenuating loss of weight and lean body mass in patients with advanced pancreatic cancer [[126](#_ENREF_126)].

Etanercept, a soluble p75 tumor necrosis factor receptor:FC (TNFR:FC) fusion protein for plasma cytokines, has been used over the last decade for the treatment of immune-mediated rheumatic diseases. In a clinical pilot study, patients with several advanced malignancies treated with etanercept combined with docetaxel had less fatigue and improved tolerability to anti-tumor treatment, although etanercept alone did not show effects [[127](#_ENREF_127)].

**Omega-3- fatty acids (n-3-FA), Eicosapentaenoic acid (EPA)**

Eicosapentaenoic acid (EPA) is one of several omega-3 polyunsaturated fatty acids found abundantly in fish oil. Polyunsaturated fatty acids have been proposed to reduce cachexia-associated tissue wasting [[128](#_ENREF_128)] as well as tumor growth [[129](#_ENREF_129), [130](#_ENREF_130)]. EPA down-regulates the production of pro-inflammatory cytokines in both healthy individuals and patients with cancer. Furthermore, the effects of proteolysis inducing factor (PIF), a cachectic factor produced by cancer, are also inhibited by EPA.

Three systematic reviews have been published regarding n-3-FA. Only one of these formulated a weak recommendation of n-3-FA for patients with advanced cancer and weight loss [[131](#_ENREF_131)], stating that there was a fair evidence to recommend its use (recommendation grade B). The other two reviews found no clear advantages from treatment with n-3-FA. A meta-analysis by Colomer et al contained 17 trials [[61](#_ENREF_61), [132-146](#_ENREF_132)], and attempted to evaluate the effectiveness and safety of n-3-FA in relieving symptoms associated with the cancer cachexia syndrome. They reported that EPA improved various clinical, biochemical, and quality of life parameters after 8 weeks of treatment [[131](#_ENREF_131)]. Dewey et al showed that data were insufficient to determine whether oral EPA is better than placebo in their analysis of 5 trials [[130](#_ENREF_130), [137](#_ENREF_137), [140](#_ENREF_140), [147](#_ENREF_147), [148](#_ENREF_148)]. Comparison of EPA versus MEGACE as an appetite stimulant provided no evidence that EPA improved cachexia-related symptoms [[149](#_ENREF_149)]. Mazzotta et al systematically reviewed several databases including publications until 2006 in order to identify the clinical efficacy of EPA and DHA for the management of cachexia in cancer patients [[150](#_ENREF_150)]. They analyzed 10 studies and 7 RCTs [[133](#_ENREF_133), [137](#_ENREF_137), [140-142](#_ENREF_140), [151](#_ENREF_151), [152](#_ENREF_152)]and found no clear advantage of either EPA or DHA on weight, lean muscle mass, symptoms, quality of life, or survival. Studies that reported statistically significant differences were found to have only a small clinical difference, not enough to justify the use of EPA or DHA alone as a treatment option. However, it does seem clear that multidimensional treatments represent the most useful approach for cachexia in advanced cancer [[150](#_ENREF_150)].

Altogether, there is not enough evidence to support a net benefit from n-3-FA in treating cachexia from advanced cancer. On the other hand, adverse effects were infrequent and not severe. More research is needed not only on drugs such as eicosapentaenoic acid or other n-3-FA, but also on multimodal approaches combining drugs and non-drug interventions.

**Herbal medicine (Kampo)**

Kampo is the Japanese herbal medical practice, which is an adaptation of traditional Chinese medicine that came to Japan between the 7th and 9th centuries. Kampo has been shown to have significant clinical benefits for cachexia [[153](#_ENREF_153)]. Fujitsuka et al reported that Rikkunshito, a Kampo formula, improved anorexia, gastrointestinal dysmotility, muscle wasting, and anxiety-related behavior [[154](#_ENREF_154)]. Rikkunshito improved anorexia-cachexia and prolonged survival of tumor-bearing rats in this study. Moreover, Rikkunshito significantly prolonged median survival of pancreatic cancer patients with ascites who were treated with gemcitabine. These studies suggest that Rikkunshito may be useful in clinical practice for cachectic cancer patients. Although the mechanisms of how the herbs demonstrate these effects are unclear and remain to be elucidated, they deserve further studies as new potential therapy agents for cancer treatment [[155](#_ENREF_155)].

**Corticosteroids**

Corticosteroids are one of the most widely used appetite stimulants. In randomized controlled studies, they have been shown to improve appetite and quality of life compared with placebo [[156](#_ENREF_156)]. MEGACE and corticosteroids seem equally effective, although for long-term use, corticosteroids result in more serious adverse effects such as protein breakdown, insulin resistance, water retention, and adrenal suppression [[157](#_ENREF_157)]. Therefore, corticosteroids are not suitable for long-term use and should be used in a limited fashion, such as during the pre-terminal phase of cachexia.

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

There are four studies investigating the relationship between NSAIDs and cancer cachexia [[158-161](#_ENREF_158)]. These studies demonstrated improved quality of life, performance status, inflammatory markers, weight gain and survival. Notably these reviews show that side effects of NSAIDs use were not remarkable in these reports that were evaluated.

However, two reports concluded data were insufficient for interpreting their widespread use of NSAIDs in practice [[162](#_ENREF_162), [163](#_ENREF_163)]. This reflection comes up from the view of the large studies heterogeneity in terms of study design, number of patients, type of cancer, clinical parameters, definition of effect criteria, and the weakness of the many individual studies.

**β2-adrenergic agonists**

β2-adrenergic agonists are potent muscle growth promoters in many animal species resulting in skeletal muscle hypertrophy [[164-167](#_ENREF_164)], and reduction of the body fat content [[168](#_ENREF_168), [169](#_ENREF_169)]. The wide variety of physiologic functions controlled by β-adrenergic receptors suggest that the mechanisms underlying effects on carcass composition may be extremely complex.

Formoterol is a long-acting β2 agonist approved for the management of asthma and chronic obstructive pulmonary disease. Formoterol exerts a selective, powerful protective action on heart and skeletal muscle by antagonizing the enhanced protein degradation, which is a characteristic of cancer cachexia. β2-agonists are also proposed to have a protective action against the apoptosis of skeletal muscle. Formoterol may be potential therapeutic tool in pathologic states [[170](#_ENREF_170)].

**Others**

Other drugs that are investigated to be used for cancer cachexia include Erythropoetin [[171-173](#_ENREF_171)], ACE inhibitors [[174](#_ENREF_174)], and β-blockers [[175](#_ENREF_175)].

**Chemotherapy**

At the present time, cancer cachexia cannot be cured. However, several recent randomized trials using combinations of newer chemotherapy agents have shown promising results. Combination chemotherapy was initially assessed with low-efficacy regimens designed for symptomatic management in the palliative setting until effective regimens were discovered that were found improve survival in the adjuvant setting [[176](#_ENREF_176)]. Regimens combining multiple drugs are expected to be successful. In a phase II study, the combined administration of anti-oxidants, pharmaco-nutritional support, progestagen and anti-cyclooxygenase-2 drugs, was shown to be safe and effective for cancer cachexia [[177](#_ENREF_177)]. Based on those results, ,an ongoing randomized phase III study began recruiting patients in 2005, with the aim of including more than 300 cachectic cancer patients. Findings to date reinforce the use of multi-modal therapies in the treatment of the cachexia-anorexia syndrome in cancer. Usually the response to therapy is better with early intervention during active adjuvant or palliative cancer therapy, compared to treatment when the patient has progressed to become refractory to anti-cachexia treatment. One of the challenges to undertaking ‘upfront’ randomized trials for cachexia is that the systemic chemotherapy for cancer treatment itself can aggravate weight loss, and for anti-cachexia therapy to show benefit it has to “compete” with chemotherapy.

**Dietary treatment**

Since cancer cachexia differs from starvation, at the present time no single modality therapies using traditionally applied nutritional regimens has succeeded in demonstrate any efﬁcacy in improving weight gain, including gain in lean body mass, in patients diagnosed with cancer cachexia [[178](#_ENREF_178)]. The average calorie deficit in weight-losing patient is reported to be approximately 200 kcal per day in the setting of advanced cancer [[132](#_ENREF_132)] and 250–400 kcals/day in those patients with cancer cachexia [[178](#_ENREF_178)]. An average supplementation of 1 calorie/mL has not been shown to improve the nutritional status of patients receiving chemotherapy [[140](#_ENREF_140), [179](#_ENREF_179)].

The average protein intake in patients with cancer cachexia is about 0.7–1.0 g/kg per day [[140](#_ENREF_140)]. Food energy intake needs to increase by 300–400 kcal per day and protein intake to increase by up to 50% to have an effect on anabolic resistance (recommended intake 1.0–1.5 g/kg per day). The analysis of a randomized trial found that in addition to oral nutritional support, the use of parenteral nutrition resulted in a short (6–8 weeks) but significant (P <0.001), prolongation of survival when nutritional goals were achieved [[180](#_ENREF_180)]. A meta-analysis of oral nutritional interventions in malnourished patients with cancer suggests that oral nutritional interventions have no effect on survival and that the effect on body weight and energy intake is inconsistent, though statistically significant improvements in some aspects of QOL may be achieved. In this study, nutritional intervention was associated with a significant increase in energy intake (430 kcal per day) and a weight gain of 1.9 kg. There was a beneficial effect on appetite and global quality of life [[181](#_ENREF_181)].

**Physical exercise**

Physical exercise has been suggested as a promising countermeasure for preventing cachexia [[182](#_ENREF_182)]. Unfortunately, only a few studies, in both clinical and experimental settings, have been performed to define the effectiveness of exercise against cachexia.

The rationale for the use of exercise is relies on the known are dramatic reduction of muscle strength and endurance during cachexia [[183-186](#_ENREF_183)]. Since it is also reported that exercise increases insulin sensitivity, protein synthesis rate, and anti-oxidative enzyme activity [[187](#_ENREF_187)] it may lead to a suppression of the inflammatory response and enhancement of immune function [[188](#_ENREF_188)]. There is significant evidence that endurance exercise (e.g., a high number of repetitions performed over extended time periods against relatively low resistance) ameliorates cancer-related fatigue [[189](#_ENREF_189)]. A randomized trial has also reported that, in patients with advanced-stage cancer, exercise is feasible and that although fatigue is not reduced, physical performance is improved significantly [[190](#_ENREF_190)]. Combination of resistance and aerobic muscle training has been suggested to be incorporated into cachexia treatment programs [[191](#_ENREF_191)]. Exercise training is able to increase both strength and endurance in healthy conditions, depending on the type of exercise, and moreover, it has been proven to act as an excellent anabolic drive for skeletal muscle in combination with anabolic steroids or other muscle anabolic drugs [[192](#_ENREF_192)].

**Future directions**

Additional directions for study in the field of cancer cachexia may come from the results of Bossola et al. [[193](#_ENREF_193)] who showed hyper-expression of mRNA for ubiquitin and increased proteolytic activity of proteasomes prior to weight loss in cancer patients. This finding could open a new research area in the field of early intervention and of prevention of cancer induced weight loss. Further research is also needed into cancer anorexia, due to the frequent finding of reduced food intake in cancer patients, and the lack of any current powerful therapies to improve appetite and daily caloric intake.

**Conclusion**

Cancer cachexia has been regarded as a non-curable disease, and has been estimated to be responsible for the death of over 20% of cancer patients. The management of cancer cachexia has improved dramatically in the past decade, as the mechanisms involved in the development and progression of the condition continue to be elucidated. Currently all treatments for cancer cachexia are considered palliative, but new agents have improved patient survival as well as their quality of life. Regular anti-neoplastic agents have ability to treat cancer, but in many cases worsen cachexia. Future progress in the field will be realized through development of treatment agents with ability to affect cancer progression as well as improve patient quality of life.

**Disclosure**

The authors have declared no conflicts of interest related to this review article.

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**References**

1 Tisdale MJ. Mechanisms of cancer cachexia. *Physiological reviews* 2009; **89**(2): 381-410 [PMID: 19342610 DOI: 10.1152/physrev.00016.2008]

2 Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nature reviews Clinical oncology* 2013; **10**(2): 90-99 [PMID: 23207794 DOI: 10.1038/nrclinonc.2012.209]

3 Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. *The lancet oncology* 2011; **12**(5): 489-495 [PMID: 21296615 DOI: 10.1016/S1470-2045(10)70218-7]

4 Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R, Anker SD. Cachexia: a new definition. *Clin Nutr* 2008; **27**(6): 793-799 [PMID: 18718696 DOI: 10.1016/j.clnu.2008.06.013]

5 Tisdale MJ. Cachexia in cancer patients. *Nature reviews Cancer* 2002; **2**(11): 862-871 [PMID: 12415256 DOI: 10.1038/nrc927]

6 Congleton J. The pulmonary cachexia syndrome: aspects of energy balance. *The Proceedings of the Nutrition Society* 1999; **58**(2): 321-328 [PMID: 10466173]

7 von Haehling S, Lainscak M, Springer J, Anker SD. Cardiac cachexia: a systematic overview. *Pharmacology & therapeutics* 2009; **121**(3): 227-252 [PMID: 19061914 DOI: 10.1016/j.pharmthera.2008.09.009]

8 Giordano A, Calvani M, Petillo O, Carteni M, Melone MR, Peluso G. Skeletal muscle metabolism in physiology and in cancer disease. *Journal of cellular biochemistry* 2003; **90**(1): 170-186 [PMID: 12938166 DOI: 10.1002/jcb.10601]

9 Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, Cohen MH, Douglass HO, Jr., Engstrom PF, Ezdinli EZ, Horton J, Johnson GJ, Moertel CG, Oken MM, Perlia C, Rosenbaum C, Silverstein MN, Skeel RT, Sponzo RW, Tormey DC. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *The American journal of medicine* 1980; **69**(4): 491-497 [PMID: 7424938]

10 Deans C, Wigmore SJ. Systemic inflammation, cachexia and prognosis in patients with cancer. *Current opinion in clinical nutrition and metabolic care* 2005; **8**(3): 265-269 [PMID: 15809528]

11 Tan BH, Fearon KC. Cachexia: prevalence and impact in medicine. *Current opinion in clinical nutrition and metabolic care* 2008; **11**(4): 400-407 [PMID: 18541999 DOI: 10.1097/MCO.0b013e328300ecc1]

12 Warren S. The immediate cause of death in cancer. *American Journal of Medical Science* 1932; **184**: 610-613

13 Skipworth RJ, Stewart GD, Dejong CH, Preston T, Fearon KC. Pathophysiology of cancer cachexia: much more than host-tumour interaction? *Clin Nutr* 2007; **26**(6): 667-676 [PMID: 17507116 DOI: 10.1016/j.clnu.2007.03.011]

14 Hopkinson JB, Wright DN, McDonald JW, Corner JL. The prevalence of concern about weight loss and change in eating habits in people with advanced cancer. *Journal of pain and symptom management* 2006; **32**(4): 322-331 [PMID: 17000349 DOI: 10.1016/j.jpainsymman.2006.05.012]

15 von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *Journal of cachexia, sarcopenia and muscle* 2010; **1**(1): 1-5 [PMID: 21475699 PMCID: 3060651 DOI: 10.1007/s13539-010-0002-6]

16 Diffee GM, Kalfas K, Al-Majid S, McCarthy DO. Altered expression of skeletal muscle myosin isoforms in cancer cachexia. *Am J Physiol-Cell Ph* 2002; **283**(5): C1376-C1382 [PMID: ISI:000178466500005 DOI: DOI 10.1152/ajpcell.00154.2002]

17 Tijerina AJ. The biochemical basis of metabolism in cancer cachexia. *Dimensions of critical care nursing : DCCN* 2004; **23**(6): 237-243 [PMID: 15586034]

18 Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. *Journal of pain and symptom management* 2007; **34**(1): 94-104 [PMID: 17509812 DOI: 10.1016/j.jpainsymman.2006.10.015]

19 Argiles JM. Cancer-associated malnutrition. *European journal of oncology nursing : the official journal of European Oncology Nursing Society* 2005; **9 Suppl 2**: S39-50 [PMID: 16437757 DOI: 10.1016/j.ejon.2005.09.006]

20 Mantovani G, Madeddu C. Cancer cachexia: medical management. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2010; **18**(1): 1-9 [PMID: 19688225 DOI: 10.1007/s00520-009-0722-3]

21 Springer J, von Haehling S, Anker SD. The need for a standardized definition for cachexia in chronic illness. *Nat Clin Pract Endoc* 2006; **2**(8): 416-417 [PMID: ISI:000239457600003 DOI: DOI 10.1038/ncpendmet0247]

22 Lainscak M, Filippatos GS, Gheorghiade M, Fonarow GC, Anker SD. Cachexia: Common, deadly, with an urgent need for precise definition and new therapies. *American Journal of Cardiology* 2008; **101**(11A): 8E-10E [PMID: ISI:000256451000003 DOI: DOI 10.1016/j.amjcard.2008.02.065]

23 Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. *Journal of internal medicine* 2010; **267**(6): 543-560 [PMID: 20210843 DOI: 10.1111/j.1365-2796.2010.02218.x]

24 Argiles JM, Busquets S, Toledo M, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. *Current opinion in supportive and palliative care* 2009; **3**(4): 263-268 [PMID: 19713854 DOI: 10.1097/SPC.0b013e3283311d09]

25 MacDonald N, Easson AM, Mazurak VC, Dunn GP, Baracos VE. Understanding and managing cancer cachexia. *Journal of the American College of Surgeons* 2003; **197**(1): 143-161 [PMID: 12831935 DOI: 10.1016/S1072-7515(03)00382-X]

26 Blum D, Omlin A, Baracos VE, Solheim TS, Tan BH, Stone P, Kaasa S, Fearon K, Strasser F. Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer. *Critical reviews in oncology/hematology* 2011; **80**(1): 114-144 [PMID: 21216616 DOI: 10.1016/j.critrevonc.2010.10.004]

27 Deans DA, Tan BH, Wigmore SJ, Ross JA, de Beaux AC, Paterson-Brown S, Fearon KC. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. *British journal of cancer* 2009; **100**(1): 63-69 [PMID: 19127266 PMCID: 2634686 DOI: 10.1038/sj.bjc.6604828]

28 Fearon KC, Barber MD, Falconer JS, McMillan DC, Ross JA, Preston T. Pancreatic cancer as a model: inflammatory mediators, acute-phase response, and cancer cachexia. *World journal of surgery* 1999; **23**(6): 584-588 [PMID: 10227928]

29 Pepys MB, Hirschfield GM, Tennent GA, Gallimore JR, Kahan MC, Bellotti V, Hawkins PN, Myers RM, Smith MD, Polara A, Cobb AJ, Ley SV, Aquilina JA, Robinson CV, Sharif I, Gray GA, Sabin CA, Jenvey MC, Kolstoe SE, Thompson D, Wood SP. Targeting C-reactive protein for the treatment of cardiovascular disease. *Nature* 2006; **440**(7088): 1217-1221 [PMID: 16642000 DOI: 10.1038/nature04672]

30 Staal-van den Brekel AJ, Dentener MA, Schols AM, Buurman WA, Wouters EF. Increased resting energy expenditure and weight loss are related to a systemic inflammatory response in lung cancer patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1995; **13**(10): 2600-2605 [PMID: 7595713]

31 Scott HR, McMillan DC, Crilly A, McArdle CS, Milroy R. The relationship between weight loss and interleukin 6 in non-small-cell lung cancer. *British journal of cancer* 1996; **73**(12): 1560-1562 [PMID: 8664130 PMCID: 2074552]

32 Blay JY, Negrier S, Combaret V, Attali S, Goillot E, Merrouche Y, Mercatello A, Ravault A, Tourani JM, Moskovtchenko JF, et al. Serum level of interleukin 6 as a prognosis factor in metastatic renal cell carcinoma. *Cancer research* 1992; **52**(12): 3317-3322 [PMID: 1596890]

33 Falconer JS, Fearon KC, Ross JA, Elton R, Wigmore SJ, Garden OJ, Carter DC. Acute-phase protein response and survival duration of patients with pancreatic cancer. *Cancer* 1995; **75**(8): 2077-2082 [PMID: 7535184]

34 O'Gorman P, McMillan DC, McArdle CS. Impact of weight loss, appetite, and the inflammatory response on quality of life in gastrointestinal cancer patients. *Nutrition and cancer* 1998; **32**(2): 76-80 [PMID: 9919615 DOI: 10.1080/01635589809514722]

35 Barber MD, Ross JA, Fearon KC. Changes in nutritional, functional, and inflammatory markers in advanced pancreatic cancer. *Nutrition and cancer* 1999; **35**(2): 106-110 [PMID: 10693162 DOI: 10.1207/S15327914NC352\_2]

36 Reeds PJ, Fjeld CR, Jahoor F. Do the differences between the amino acid compositions of acute-phase and muscle proteins have a bearing on nitrogen loss in traumatic states? *The Journal of nutrition* 1994; **124**(6): 906-910 [PMID: 7515956]

37 Barber MD, Fearon KC, McMillan DC, Slater C, Ross JA, Preston T. Liver export protein synthetic rates are increased by oral meal feeding in weight-losing cancer patients. *American journal of physiology Endocrinology and metabolism* 2000; **279**(3): E707-714 [PMID: 10950840]

38 Ross JA, Fearon KC. Eicosanoid-dependent cancer cachexia and wasting. *Current opinion in clinical nutrition and metabolic care* 2002; **5**(3): 241-248 [PMID: 11953648]

39 Tisdale MJ. The 'cancer cachectic factor'. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2003; **11**(2): 73-78 [PMID: 12560934 DOI: 10.1007/s00520-002-0408-6]

40 Baracos VE, Mazurak VC, Ma DW. n-3 Polyunsaturated fatty acids throughout the cancer trajectory: influence on disease incidence, progression, response to therapy and cancer-associated cachexia. *Nutrition research reviews* 2004; **17**(2): 177-192 [PMID: 19079925 DOI: 10.1079/NRR200488]

41 Zhou X, Wang JL, Lu J, Song Y, Kwak KS, Jiao Q, Rosenfeld R, Chen Q, Boone T, Simonet WS, Lacey DL, Goldberg AL, Han HQ. Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. *Cell* 2010; **142**(4): 531-543 [PMID: 20723755 DOI: 10.1016/j.cell.2010.07.011]

42 Benny Klimek ME, Aydogdu T, Link MJ, Pons M, Koniaris LG, Zimmers TA. Acute inhibition of myostatin-family proteins preserves skeletal muscle in mouse models of cancer cachexia. *Biochemical and biophysical research communications* 2010; **391**(3): 1548-1554 [PMID: 20036643 DOI: 10.1016/j.bbrc.2009.12.123]

43 Murphy KT, Chee A, Gleeson BG, Naim T, Swiderski K, Koopman R, Lynch GS. Antibody-directed myostatin inhibition enhances muscle mass and function in tumor-bearing mice. *American journal of physiology Regulatory, integrative and comparative physiology* 2011; **301**(3): R716-726 [PMID: 21677277 DOI: 10.1152/ajpregu.00121.2011]

44 Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. *Cell metabolism* 2012; **16**(2): 153-166 [PMID: 22795476 DOI: 10.1016/j.cmet.2012.06.011]

45 Dodson S, Baracos VE, Jatoi A, Evans WJ, Cella D, Dalton JT, Steiner MS. Muscle wasting in cancer cachexia: clinical implications, diagnosis, and emerging treatment strategies. *Annual review of medicine* 2011; **62**: 265-279 [PMID: 20731602 DOI: 10.1146/annurev-med-061509-131248]

46 Carson JA, Baltgalvis KA. Interleukin 6 as a key regulator of muscle mass during cachexia. *Exercise and sport sciences reviews* 2010; **38**(4): 168-176 [PMID: 20871233 PMCID: 3065300 DOI: 10.1097/JES.0b013e3181f44f11]

47 Haslett PA. Anticytokine approaches to the treatment of anorexia and cachexia. *Seminars in oncology* 1998; **25**(2 Suppl 6): 53-57 [PMID: 9625384]

48 Mantovani G, Maccio A, Lai P, Massa E, Ghiani M, Santona MC. Cytokine activity in cancer-related anorexia/cachexia: role of megestrol acetate and medroxyprogesterone acetate. *Seminars in oncology* 1998; **25**(2 Suppl 6): 45-52 [PMID: 9625383]

49 Tisdale MJ. Biology of cachexia. *Journal of the National Cancer Institute* 1997; **89**(23): 1763-1773 [PMID: 9392617]

50 Plata-Salaman CR. Immunoregulators in the nervous system. *Neuroscience and biobehavioral reviews* 1991; **15**(2): 185-215 [PMID: 1852312]

51 Plata-Salaman CR. Anorexia during acute and chronic disease. *Nutrition* 1996; **12**(2): 69-78 [PMID: 8724375]

52 Moldawer LL, Copeland EM, 3rd. Proinflammatory cytokines, nutritional support, and the cachexia syndrome: interactions and therapeutic options. *Cancer* 1997; **79**(9): 1828-1839 [PMID: 9129003]

53 Banks WA. Anorectic effects of circulating cytokines: role of the vascular blood-brain barrier. *Nutrition* 2001; **17**(5): 434-437 [PMID: 11377145]

54 Hellerstein MK, Meydani SN, Meydani M, Wu K, Dinarello CA. Interleukin-1-induced anorexia in the rat. Influence of prostaglandins. *The Journal of clinical investigation* 1989; **84**(1): 228-235 [PMID: 2786888 PMCID: 303974 DOI: 10.1172/JCI114145]

55 Torelli GF, Meguid MM, Moldawer LL, Edwards CK, 3rd, Kim HJ, Carter JL, Laviano A, Rossi Fanelli F. Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. *The American journal of physiology* 1999; **277**(3 Pt 2): R850-855 [PMID: 10484503]

56 Yeh SS, Schuster MW. Geriatric cachexia: the role of cytokines. *The American journal of clinical nutrition* 1999; **70**(2): 183-197 [PMID: 10426694]

57 Laviano A, Meguid MM, Yang ZJ, Gleason JR, Cangiano C, Rossi Fanelli F. Cracking the riddle of cancer anorexia. *Nutrition* 1996; **12**(10): 706-710 [PMID: 8936495]

58 Picton SV. Aspects of altered metabolism in children with cancer. *International journal of cancer Supplement = Journal international du cancer Supplement* 1998; **11**: 62-64 [PMID: 9876481]

59 Albrecht JT, Canada TW. Cachexia and anorexia in malignancy. *Hematology/oncology clinics of North America* 1996; **10**(4): 791-800 [PMID: 8811301]

60 Mihara M, Hashizume M, Yoshida H, Suzuki M, Shiina M. IL-6/IL-6 receptor system and its role in physiological and pathological conditions. *Clin Sci (Lond)* 2012; **122**(4): 143-159 [PMID: 22029668 DOI: 10.1042/CS20110340]

61 Barber MD, Fearon KC, Tisdale MJ, McMillan DC, Ross JA. Effect of a fish oil-enriched nutritional supplement on metabolic mediators in patients with pancreatic cancer cachexia. *Nutrition and cancer* 2001; **40**(2): 118-124 [PMID: 11962246 DOI: 10.1207/S15327914NC402\_7]

62 Socher SH, Martinez D, Craig JB, Kuhn JG, Oliff A. Tumor necrosis factor not detectable in patients with clinical cancer cachexia. *Journal of the National Cancer Institute* 1988; **80**(8): 595-598 [PMID: 3373550]

63 Falconer JS, Ross JA, Fearon KC, Hawkins RA, O'Riordain MG, Carter DC. Effect of eicosapentaenoic acid and other fatty acids on the growth in vitro of human pancreatic cancer cell lines. *British journal of cancer* 1994; **69**(5): 826-832 [PMID: 8180010 PMCID: 1968911]

64 Spitzner M, Ebner R, Wolff HA, Ghadimi BM, Wienands J, Grade M. STAT3: A Novel Molecular Mediator of Resistance to Chemoradiotherapy. *Cancers* 2014; **6**(4): 1986-2011 [PMID: 25268165 DOI: 10.3390/cancers6041986]

65 Bonetto A, Aydogdu T, Jin X, Zhang Z, Zhan R, Puzis L, Koniaris LG, Zimmers TA. JAK/STAT3 pathway inhibition blocks skeletal muscle wasting downstream of IL-6 and in experimental cancer cachexia. *American journal of physiology Endocrinology and metabolism* 2012; **303**(3): E410-421 [PMID: 22669242 PMCID: 3423125 DOI: 10.1152/ajpendo.00039.2012]

66 Donohoe CL, Ryan AM, Reynolds JV. Cancer cachexia: mechanisms and clinical implications. *Gastroenterology research and practice* 2011; **2011**: 601434 [PMID: 21760776 PMCID: 3132494 DOI: 10.1155/2011/601434]

67 Argiles JM, Moore-Carrasco R, Fuster G, Busquets S, Lopez-Soriano FJ. Cancer cachexia: the molecular mechanisms. *The international journal of biochemistry & cell biology* 2003; **35**(4): 405-409 [PMID: 12565701]

68 Moley JF, Aamodt R, Rumble W, Kaye W, Norton JA. Body cell mass in cancer-bearing and anorexic patients. *JPEN Journal of parenteral and enteral nutrition* 1987; **11**(3): 219-222 [PMID: 3474427]

69 Dworzak F, Ferrari P, Gavazzi C, Maiorana C, Bozzetti F. Effects of cachexia due to cancer on whole body and skeletal muscle protein turnover. *Cancer* 1998; **82**(1): 42-48 [PMID: 9428478]

70 Tisdale MJ. Loss of skeletal muscle in cancer: biochemical mechanisms. *Frontiers in bioscience : a journal and virtual library* 2001; **6**: D164-174 [PMID: 11171557]

71 Acharyya S, Ladner KJ, Nelsen LL, Damrauer J, Reiser PJ, Swoap S, Guttridge DC. Cancer cachexia is regulated by selective targeting of skeletal muscle gene products. *The Journal of clinical investigation* 2004; **114**(3): 370-378 [PMID: 15286803 PMCID: 484974 DOI: 10.1172/JCI20174]

72 Vaughan VC, Martin P, Lewandowski PA. Cancer cachexia: impact, mechanisms and emerging treatments. *Journal of cachexia, sarcopenia and muscle* 2013; **4**(2): 95-109 [PMID: 23097000 PMCID: 3684701 DOI: 10.1007/s13539-012-0087-1]

73 Fredrix EW, Soeters PB, Wouters EF, Deerenberg IM, von Meyenfeldt MF, Saris WH. Effect of different tumor types on resting energy expenditure. *Cancer research* 1991; **51**(22): 6138-6141 [PMID: 1657379]

74 Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. *Annals of surgery* 1994; **219**(4): 325-331 [PMID: 7512810 PMCID: 1243147]

75 Rigaud D, Hassid J, Meulemans A, Poupard AT, Boulier A. A paradoxical increase in resting energy expenditure in malnourished patients near death: the king penguin syndrome. *The American journal of clinical nutrition* 2000; **72**(2): 355-360 [PMID: 10919927]

76 Shellock FG, Riedinger MS, Fishbein MC. Brown adipose tissue in cancer patients: possible cause of cancer-induced cachexia. *Journal of cancer research and clinical oncology* 1986; **111**(1): 82-85 [PMID: 3949854]

77 Qualliotine-Mann D, Agwu DE, Ellenburg MD, McCall CE, McPhail LC. Phosphatidic acid and diacylglycerol synergize in a cell-free system for activation of NADPH oxidase from human neutrophils. *The Journal of biological chemistry* 1993; **268**(32): 23843-23849 [PMID: 8226922]

78 Bing C, Brown M, King P, Collins P, Tisdale MJ, Williams G. Increased gene expression of brown fat uncoupling protein (UCP)1 and skeletal muscle UCP2 and UCP3 in MAC16-induced cancer cachexia. *Cancer research* 2000; **60**(9): 2405-2410 [PMID: 10811117]

79 Collins P, Bing C, McCulloch P, Williams G. Muscle UCP-3 mRNA levels are elevated in weight loss associated with gastrointestinal adenocarcinoma in humans. *British journal of cancer* 2002; **86**(3): 372-375 [PMID: 11875702 PMCID: 2375209 DOI: 10.1038/sj.bjc.6600074]

80 Loprinzi CL, Michalak JC, Schaid DJ, Mailliard JA, Athmann LM, Goldberg RM, Tschetter LK, Hatfield AK, Morton RF. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1993; **11**(4): 762-767 [PMID: 8478668]

81 Bruera E, Macmillan K, Kuehn N, Hanson J, MacDonald RN. A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status, and other symptoms in patients with advanced cancer. *Cancer* 1990; **66**(6): 1279-1282 [PMID: 2205358]

82 Neri B, Garosi VL, Intini C. Effect of medroxyprogesterone acetate on the quality of life of the oncologic patient: a multicentric cooperative study. *Anti-cancer drugs* 1997; **8**(5): 459-465 [PMID: 9215608]

83 Nelson KA. The cancer anorexia-cachexia syndrome. *Seminars in oncology* 2000; **27**(1): 64-68 [PMID: 10697022]

84 Gagnon B, Bruera E. A review of the drug treatment of cachexia associated with cancer. *Drugs* 1998; **55**(5): 675-688 [PMID: 9585863]

85 Argiles JM, Meijsing SH, Pallares-Trujillo J, Guirao X, Lopez-Soriano FJ. Cancer cachexia: a therapeutic approach. *Medicinal research reviews* 2001; **21**(1): 83-101 [PMID: 11135301]

86 Feliu J, Gonzalez-Baron M, Berrocal A, Ordonez A, Baron-Saura JM. Treatment of cancer anorexia with megestrol acetate: which is the optimal dose? *Journal of the National Cancer Institute* 1991; **83**(6): 449-450 [PMID: 1999853]

87 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**(13): 1127-1132 [PMID: 2193166]

88 Tchekmedyian NS, Hickman M, Siau J, Greco FA, Keller J, Browder H, Aisner J. Megestrol acetate in cancer anorexia and weight loss. *Cancer* 1992; **69**(5): 1268-1274 [PMID: 1739926]

89 Loprinzi CL, Schaid DJ, Dose AM, Burnham NL, Jensen MD. Body-composition changes in patients who gain weight while receiving megestrol acetate. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1993; **11**(1): 152-154 [PMID: 8418227]

90 Rowland KM, Jr., Loprinzi CL, Shaw EG, Maksymiuk AW, Kuross SA, Jung SH, Kugler JW, Tschetter LK, Ghosh C, Schaefer PL, Owen D, Washburn JH, Jr., Webb TA, Mailliard JA, Jett JR. Randomized double-blind placebo-controlled trial of cisplatin and etoposide plus megestrol acetate/placebo in extensive-stage small-cell lung cancer: a North Central Cancer Treatment Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1996; **14**(1): 135-141 [PMID: 8558188]

91 Ruiz Garcia V, Lopez-Briz E, Carbonell Sanchis R, Gonzalvez Perales JL, Bort-Marti S. Megestrol acetate for treatment of anorexia-cachexia syndrome. *The Cochrane database of systematic reviews* 2013; **3**: CD004310 [PMID: 23543530 DOI: 10.1002/14651858.CD004310.pub3]

92 McCarthy HD, Crowder RE, Dryden S, Williams G. Megestrol acetate stimulates food and water intake in the rat: effects on regional hypothalamic neuropeptide Y concentrations. *European journal of pharmacology* 1994; **265**(1-2): 99-102 [PMID: 7883035]

93 Mantovani G, Maccio A, Massa E, Madeddu C. Managing cancer-related anorexia/cachexia. *Drugs* 2001; **61**(4): 499-514 [PMID: 11324680]

94 Maltoni M, Nanni O, Scarpi E, Rossi D, Serra P, Amadori D. High-dose progestins for the treatment of cancer anorexia-cachexia syndrome: a systematic review of randomised clinical trials. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2001; **12**(3): 289-300 [PMID: 11332139]

95 Mantovani G, Maccio A, Esu S, Lai P, Santona MC, Massa E, Dessi D, Melis GB, Del Giacco GS. Medroxyprogesterone acetate reduces the in vitro production of cytokines and serotonin involved in anorexia/cachexia and emesis by peripheral blood mononuclear cells of cancer patients. *Eur J Cancer* 1997; **33**(4): 602-607 [PMID: 9274442]

96 Costa AM, Spence KT, Plata-Salaman CR, ffrench-Mullen JM. Residual Ca2+ channel current modulation by megestrol acetate via a G-protein alpha s-subunit in rat hypothalamic neurones. *The Journal of physiology* 1995; **487 ( Pt 2)**: 291-303 [PMID: 8558464 PMCID: 1156573]

97 Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999; **402**(6762): 656-660 [PMID: 10604470 DOI: 10.1038/45230]

98 Cheung CK, Wu JC. Role of ghrelin in the pathophysiology of gastrointestinal disease. *Gut and liver* 2013; **7**(5): 505-512 [PMID: 24073306 PMCID: 3782663 DOI: 10.5009/gnl.2013.7.5.505]

99 Hanada T, Toshinai K, Date Y, Kajimura N, Tsukada T, Hayashi Y, Kangawa K, Nakazato M. Upregulation of ghrelin expression in cachectic nude mice bearing human melanoma cells. *Metabolism: clinical and experimental* 2004; **53**(1): 84-88 [PMID: 14681847]

100 Kerem M, Ferahkose Z, Yilmaz UT, Pasaoglu H, Ofluoglu E, Bedirli A, Salman B, Sahin TT, Akin M. Adipokines and ghrelin in gastric cancer cachexia. *World journal of gastroenterology : WJG* 2008; **14**(23): 3633-3641 [PMID: 18595130 PMCID: 2719226]

101 Takahashi M, Terashima M, Takagane A, Oyama K, Fujiwara H, Wakabayashi G. Ghrelin and leptin levels in cachectic patients with cancer of the digestive organs. *International journal of clinical oncology* 2009; **14**(4): 315-320 [PMID: 19705241 DOI: 10.1007/s10147-008-0856-1]

102 Shimizu Y, Nagaya N, Isobe T, Imazu M, Okumura H, Hosoda H, Kojima M, Kangawa K, Kohno N. Increased plasma ghrelin level in lung cancer cachexia. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2003; **9**(2): 774-778 [PMID: 12576449]

103 Karapanagiotou EM, Polyzos A, Dilana KD, Gratsias I, Boura P, Gkiozos I, Syrigos KN. Increased serum levels of ghrelin at diagnosis mediate body weight loss in non-small cell lung cancer (NSCLC) patients. *Lung Cancer* 2009; **66**(3): 393-398 [PMID: 19282046 DOI: 10.1016/j.lungcan.2009.02.006]

104 Garcia JM, Garcia-Touza M, Hijazi RA, Taffet G, Epner D, Mann D, Smith RG, Cunningham GR, Marcelli M. Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. *The Journal of clinical endocrinology and metabolism* 2005; **90**(5): 2920-2926 [PMID: 15713718 DOI: 10.1210/jc.2004-1788]

105 Nagaya N, Kojima M, Kangawa K. Ghrelin, a novel growth hormone-releasing peptide, in the treatment of cardiopulmonary-associated cachexia. *Intern Med* 2006; **45**(3): 127-134 [PMID: 16508225]

106 Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. *CA: a cancer journal for clinicians* 2002; **52**(2): 72-91 [PMID: 11929007]

107 Gorter RW. Cancer cachexia and cannabinoids. *Forschende Komplementarmedizin* 1999; **6 Suppl 3**: 21-22 [PMID: 10575285 DOI: 57152]

108 Mitchelson F. Pharmacological agents affecting emesis. A review (Part II). *Drugs* 1992; **43**(4): 443-463 [PMID: 1377113]

109 Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, Pundaleeka S, Kardinal CG, Fitch TR, Krook JE, Novotny PJ, Christensen B. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2002; **20**(2): 567-573 [PMID: 11786587]

110 Strasser F, Luftner D, Possinger K, Ernst G, Ruhstaller T, Meissner W, Ko YD, Schnelle M, Reif M, Cerny T. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**(21): 3394-3400 [PMID: 16849753 DOI: 10.1200/JCO.2005.05.1847]

111 Marks DL, Butler AA, Turner R, Brookhart G, Cone RD. Differential role of melanocortin receptor subtypes in cachexia. *Endocrinology* 2003; **144**(4): 1513-1523 [PMID: 12639936 DOI: 10.1210/en.2002-221099]

112 Scarlett JM, Marks DL. The use of melanocortin antagonists in cachexia of chronic disease. *Expert opinion on investigational drugs* 2005; **14**(10): 1233-1239 [PMID: 16185165 DOI: 10.1517/13543784.14.10.1233]

113 DeBoer MD, Marks DL. Therapy insight: Use of melanocortin antagonists in the treatment of cachexia in chronic disease. *Nature clinical practice Endocrinology & metabolism* 2006; **2**(8): 459-466 [PMID: 16932335 DOI: 10.1038/ncpendmet0221]

114 Oliff A, Defeo-Jones D, Boyer M, Martinez D, Kiefer D, Vuocolo G, Wolfe A, Socher SH. Tumors secreting human TNF/cachectin induce cachexia in mice. *Cell* 1987; **50**(4): 555-563 [PMID: 3607879]

115 Langstein HN, Doherty GM, Fraker DL, Buresh CM, Norton JA. The roles of gamma-interferon and tumor necrosis factor alpha in an experimental rat model of cancer cachexia. *Cancer research* 1991; **51**(9): 2302-2306 [PMID: 1901758]

116 Strassmann G, Fong M, Kenney JS, Jacob CO. Evidence for the involvement of interleukin 6 in experimental cancer cachexia. *The Journal of clinical investigation* 1992; **89**(5): 1681-1684 [PMID: 1569207 PMCID: 443047 DOI: 10.1172/JCI115767]

117 Costelli P, Carbo N, Tessitore L, Bagby GJ, Lopez-Soriano FJ, Argiles JM, Baccino FM. Tumor necrosis factor-alpha mediates changes in tissue protein turnover in a rat cancer cachexia model. *The Journal of clinical investigation* 1993; **92**(6): 2783-2789 [PMID: 8254032 PMCID: 288478 DOI: 10.1172/JCI116897]

118 Murray S, Schell K, McCarthy DO, Albertini MR. Tumor growth, weight loss and cytokines in SCID mice. *Cancer letters* 1997; **111**(1-2): 111-115 [PMID: 9022135]

119 Matthys P, Heremans H, Opdenakker G, Billiau A. Anti-interferon-gamma antibody treatment, growth of Lewis lung tumours in mice and tumour-associated cachexia. *Eur J Cancer* 1991; **27**(2): 182-187 [PMID: 1827286]

120 Strassmann G, Kambayashi T. Inhibition of experimental cancer cachexia by anti-cytokine and anti-cytokine-receptor therapy. *Cytokines and molecular therapy* 1995; **1**(2): 107-113 [PMID: 9384667]

121 Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: cytokines and neuropeptides. *Current opinion in clinical nutrition and metabolic care* 2004; **7**(4): 427-434 [PMID: 15192446]

122 Inui A. Cancer anorexia-cachexia syndrome: are neuropeptides the key? *Cancer research* 1999; **59**(18): 4493-4501 [PMID: 10493494]

123 Yamamoto N, Kawamura I, Nishigaki F, Tsujimoto S, Naoe Y, Inami M, Elizabeth L, Manda T, Shimomura K. Effect of FR143430, a novel cytokine suppressive agent, on adenocarcinoma colon26-induced cachexia in mice. *Anticancer research* 1998; **18**(1A): 139-144 [PMID: 9568068]

124 Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *The Journal of experimental medicine* 1991; **173**(3): 699-703 [PMID: 1997652 PMCID: 2118820]

125 Gordon JN, Goggin PM. Thalidomide and its derivatives: emerging from the wilderness. *Postgraduate medical journal* 2003; **79**(929): 127-132 [PMID: 12697909 PMCID: 1742651]

126 Gordon JN, Trebble TM, Ellis RD, Duncan HD, Johns T, Goggin PM. Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005; **54**(4): 540-545 [PMID: 15753541 PMCID: 1774430 DOI: 10.1136/gut.2004.047563]

127 Monk JP, Phillips G, Waite R, Kuhn J, Schaaf LJ, Otterson GA, Guttridge D, Rhoades C, Shah M, Criswell T, Caligiuri MA, Villalona-Calero MA. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**(12): 1852-1859 [PMID: 16622259 DOI: 10.1200/JCO.2005.04.2838]

128 Tisdale MJ. Mechanism of lipid mobilization associated with cancer cachexia: interaction between the polyunsaturated fatty acid, eicosapentaenoic acid, and inhibitory guanine nucleotide-regulatory protein. *Prostaglandins, leukotrienes, and essential fatty acids* 1993; **48**(1): 105-109 [PMID: 8380931]

129 Anti M, Marra G, Armelao F, Bartoli GM, Ficarelli R, Percesepe A, De Vitis I, Maria G, Sofo L, Rapaccini GL, et al. Effect of omega-3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. *Gastroenterology* 1992; **103**(3): 883-891 [PMID: 1386825]

130 Rose DP, Connolly JM. Effects of dietary omega-3 fatty acids on human breast cancer growth and metastases in nude mice. *Journal of the National Cancer Institute* 1993; **85**(21): 1743-1747 [PMID: 8411258]

131 Colomer R, Moreno-Nogueira JM, Garcia-Luna PP, Garcia-Peris P, Garcia-de-Lorenzo A, Zarazaga A, Quecedo L, del Llano J, Usan L, Casimiro C. N-3 fatty acids, cancer and cachexia: a systematic review of the literature. *The British journal of nutrition* 2007; **97**(5): 823-831 [PMID: 17408522 DOI: 10.1017/S000711450765795X]

132 Moses AW, Slater C, Preston T, Barber MD, Fearon KC. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. *British journal of cancer* 2004; **90**(5): 996-1002 [PMID: 14997196 PMCID: 2409623 DOI: 10.1038/sj.bjc.6601620]

133 Barber MD, Ross JA, Preston T, Shenkin A, Fearon KC. Fish oil-enriched nutritional supplement attenuates progression of the acute-phase response in weight-losing patients with advanced pancreatic cancer. *The Journal of nutrition* 1999; **129**(6): 1120-1125 [PMID: 10356075]

134 Barber MD, Ross JA, Voss AC, Tisdale MJ, Fearon KC. The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. *British journal of cancer* 1999; **81**(1): 80-86 [PMID: 10487616 PMCID: 2374349 DOI: 10.1038/sj.bjc.6690654]

135 Barber MD, McMillan DC, Preston T, Ross JA, Fearon KC. Metabolic response to feeding in weight-losing pancreatic cancer patients and its modulation by a fish-oil-enriched nutritional supplement. *Clin Sci (Lond)* 2000; **98**(4): 389-399 [PMID: 10731472]

136 Barber MD, Fearon KC. Tolerance and incorporation of a high-dose eicosapentaenoic acid diester emulsion by patients with pancreatic cancer cachexia. *Lipids* 2001; **36**(4): 347-351 [PMID: 11383684]

137 Bruera E, Strasser F, Palmer JL, Willey J, Calder K, Amyotte G, Baracos V. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2003; **21**(1): 129-134 [PMID: 12506181]

138 Burns CP, Halabi S, Clamon GH, Hars V, Wagner BA, Hohl RJ, Lester E, Kirshner JJ, Vinciguerra V, Paskett E. Phase I clinical study of fish oil fatty acid capsules for patients with cancer cachexia: cancer and leukemia group B study 9473. *Clinical cancer research : an official journal of the American Association for Cancer Research* 1999; **5**(12): 3942-3947 [PMID: 10632323]

139 Burns CP, Halabi S, Clamon G, Kaplan E, Hohl RJ, Atkins JN, Schwartz MA, Wagner BA, Paskett E. Phase II study of high-dose fish oil capsules for patients with cancer-related cachexia. *Cancer* 2004; **101**(2): 370-378 [PMID: 15241836 DOI: 10.1002/cncr.20362]

140 Fearon KC, Von Meyenfeldt MF, Moses AG, Van Geenen R, Roy A, Gouma DJ, Giacosa A, Van Gossum A, Bauer J, Barber MD, Aaronson NK, Voss AC, Tisdale MJ. 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**(10): 1479-1486 [PMID: 12970142 PMCID: 1773823]

141 Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. 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**(2): 395-402 [PMID: 9445198]

142 Jatoi A, Rowland K, Loprinzi CL, Sloan JA, Dakhil SR, MacDonald N, Gagnon B, Novotny PJ, Mailliard JA, Bushey TI, Nair S, Christensen B. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2004; **22**(12): 2469-2476 [PMID: 15197210 DOI: 10.1200/JCO.2004.06.024]

143 Kenler AS, Swails WS, Driscoll DF, DeMichele SJ, Daley B, Babineau TJ, Peterson MB, Bistrian BR. Early enteral feeding in postsurgical cancer patients. Fish oil structured lipid-based polymeric formula versus a standard polymeric formula. *Annals of surgery* 1996; **223**(3): 316-333 [PMID: 8604913 PMCID: 1235121]

144 Swails WS, Kenler AS, Driscoll DF, DeMichele SJ, Babineau TJ, Utsunamiya T, Chavali S, Forse RA, Bistrian BR. Effect of a fish oil structured lipid-based diet on prostaglandin release from mononuclear cells in cancer patients after surgery. *JPEN Journal of parenteral and enteral nutrition* 1997; **21**(5): 266-274 [PMID: 9323688]

145 Wigmore SJ, Ross JA, Falconer JS, Plester CE, Tisdale MJ, Carter DC, Fearon KC. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. *Nutrition* 1996; **12**(1 Suppl): S27-30 [PMID: 8850216]

146 Wigmore SJ, Barber MD, Ross JA, Tisdale MJ, Fearon KC. Effect of oral eicosapentaenoic acid on weight loss in patients with pancreatic cancer. *Nutrition and cancer* 2000; **36**(2): 177-184 [PMID: 10890028 DOI: 10.1207/S15327914NC3602\_6]

147 Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *International journal of cardiology* 2002; **86**(2-3): 123-130 [PMID: 12419548]

148 Zuijdgeest-Van Leeuwen SD, Dagnelie PC, Wattimena JL, Van den Berg JW, Van der Gaast A, Swart GR, Wilson JH. Eicosapentaenoic acid ethyl ester supplementation in cachectic cancer patients and healthy subjects: effects on lipolysis and lipid oxidation. *Clin Nutr* 2000; **19**(6): 417-423 [PMID: 11104593 DOI: 10.1054/clnu.2000.0162]

149 Dewey A, Baughan C, Dean T, Higgins B, Johnson I. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *The Cochrane database of systematic reviews* 2007(1): CD004597 [PMID: 17253515 DOI: 10.1002/14651858.CD004597.pub2]

150 Mazzotta P, Jeney CM. Anorexia-cachexia syndrome: a systematic review of the role of dietary polyunsaturated Fatty acids in the management of symptoms, survival, and quality of life. *Journal of pain and symptom management* 2009; **37**(6): 1069-1077 [PMID: 19054647 DOI: 10.1016/j.jpainsymman.2008.06.005]

151 Persson C, Glimelius B, Ronnelid J, Nygren P. Impact of fish oil and melatonin on cachexia in patients with advanced gastrointestinal cancer: a randomized pilot study. *Nutrition* 2005; **21**(2): 170-178 [PMID: 15723745 DOI: 10.1016/j.nut.2004.05.026]

152 Fearon KC, Barber MD, Moses AG, Ahmedzai SH, Taylor GS, Tisdale MJ, Murray GD. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**(21): 3401-3407 [PMID: 16849754 DOI: 10.1200/JCO.2005.04.5724]

153 Olaku O, White JD. Herbal therapy use by cancer patients: a literature review on case reports. *Eur J Cancer* 2011; **47**(4): 508-514 [PMID: 21185719 PMCID: 3057114 DOI: 10.1016/j.ejca.2010.11.018]

154 Fujitsuka N, Asakawa A, Uezono Y, Minami K, Yamaguchi T, Niijima A, Yada T, Maejima Y, Sedbazar U, Sakai T, Hattori T, Kase Y, Inui A. Potentiation of ghrelin signaling attenuates cancer anorexia-cachexia and prolongs survival. *Translational psychiatry* 2011; **1**: e23 [PMID: 22832525 PMCID: 3309517 DOI: 10.1038/tp.2011.25]

155 Huang CF, Lin SS, Liao PH, Young SC, Yang CC. The immunopharmaceutical effects and mechanisms of herb medicine. *Cellular & molecular immunology* 2008; **5**(1): 23-31 [PMID: 18318991 DOI: 10.1038/cmi.2008.3]

156 Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer* 1974; **33**(6): 1607-1609 [PMID: 4135151]

157 Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, Krook JE, Wilwerding MB, Rowland KM, Jr., Camoriano JK, Novotny PJ, Christensen BJ. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1999; **17**(10): 3299-3306 [PMID: 10506633]

158 Lai V, George J, Richey L, Kim HJ, Cannon T, Shores C, Couch M. Results of a pilot study of the effects of celecoxib on cancer cachexia in patients with cancer of the head, neck, and gastrointestinal tract. *Head & neck* 2008; **30**(1): 67-74 [PMID: 17615567 DOI: 10.1002/hed.20662]

159 McMillan DC, Wigmore SJ, Fearon KC, O'Gorman P, Wright CE, McArdle CS. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. *British journal of cancer* 1999; **79**(3-4): 495-500 [PMID: 10027319 PMCID: 2362415 DOI: 10.1038/sj.bjc.6690077]

160 Cerchietti LC, Navigante AH, Castro MA. Effects of eicosapentaenoic and docosahexaenoic n-3 fatty acids from fish oil and preferential Cox-2 inhibition on systemic syndromes in patients with advanced lung cancer. *Nutrition and cancer* 2007; **59**(1): 14-20 [PMID: 17927497 DOI: 10.1080/01635580701365068]

161 Lundholm K, Gelin J, Hyltander A, Lonnroth C, Sandstrom R, Svaninger G, Korner U, Gulich M, Karrefors I, Norli B, et al. Anti-inflammatory treatment may prolong survival in undernourished patients with metastatic solid tumors. *Cancer research* 1994; **54**(21): 5602-5606 [PMID: 7923204]

162 Reid J, Hughes CM, Murray LJ, Parsons C, Cantwell MM. Non-steroidal anti-inflammatory drugs for the treatment of cancer cachexia: a systematic review. *Palliative medicine* 2013; **27**(4): 295-303 [PMID: 22450159 DOI: 10.1177/0269216312441382]

163 Solheim TS, Fearon KC, Blum D, Kaasa S. Non-steroidal anti-inflammatory treatment in cancer cachexia: a systematic literature review. *Acta Oncol* 2013; **52**(1): 6-17 [PMID: 23020528 DOI: 10.3109/0284186X.2012.724536]

164 Kim YS, Sainz RD. Beta-adrenergic agonists and hypertrophy of skeletal muscles. *Life sciences* 1992; **50**(6): 397-407 [PMID: 1346465]

165 Agbenyega ET, Wareham AC. Effect of clenbuterol on skeletal muscle atrophy in mice induced by the glucocorticoid dexamethasone. *Comparative biochemistry and physiology Comparative physiology* 1992; **102**(1): 141-145 [PMID: 1351811]

166 Rajab P, Fox J, Riaz S, Tomlinson D, Ball D, Greenhaff PL. Skeletal muscle myosin heavy chain isoforms and energy metabolism after clenbuterol treatment in the rat. *American journal of physiology Regulatory, integrative and comparative physiology* 2000; **279**(3): R1076-1081 [PMID: 10956268]

167 Hinkle RT, Hodge KM, Cody DB, Sheldon RJ, Kobilka BK, Isfort RJ. Skeletal muscle hypertrophy and anti-atrophy effects of clenbuterol are mediated by the beta2-adrenergic receptor. *Muscle & nerve* 2002; **25**(5): 729-734 [PMID: 11994968 DOI: 10.1002/mus.10092]

168 Yang YT, McElligott MA. Multiple actions of beta-adrenergic agonists on skeletal muscle and adipose tissue. *The Biochemical journal* 1989; **261**(1): 1-10 [PMID: 2570567 PMCID: 1138772]

169 Mersmann HJ. Overview of the effects of beta-adrenergic receptor agonists on animal growth including mechanisms of action. *Journal of animal science* 1998; **76**(1): 160-172 [PMID: 9464897]

170 Busquets S, Figueras MT, Fuster G, Almendro V, Moore-Carrasco R, Ametller E, Argiles JM, Lopez-Soriano FJ. Anticachectic effects of formoterol: a drug for potential treatment of muscle wasting. *Cancer research* 2004; **64**(18): 6725-6731 [PMID: 15374990 DOI: 10.1158/0008-5472.CAN-04-0425]

171 Penna F, Busquets S, Toledo M, Pin F, Massa D, Lopez-Soriano FJ, Costelli P, Argiles JM. Erythropoietin administration partially prevents adipose tissue loss in experimental cancer cachexia models. *Journal of lipid research* 2013; **54**(11): 3045-3051 [PMID: 23966665 PMCID: 3793608 DOI: 10.1194/jlr.M038406]

172 van Halteren HK, Bongaerts GP, Verhagen CA, Kamm YJ, Willems JL, Grutters GJ, Koopman JP, Wagener DJ. Recombinant human erythropoietin attenuates weight loss in a murine cancer cachexia model. *Journal of cancer research and clinical oncology* 2004; **130**(4): 211-216 [PMID: 14745550 DOI: 10.1007/s00432-003-0526-7]

173 Kanzaki M, Soda K, Gin PT, Kai T, Konishi F, Kawakami M. Erythropoietin attenuates cachectic events and decreases production of interleukin-6, a cachexia-inducing cytokine. *Cytokine* 2005; **32**(5): 234-239 [PMID: 16338141 DOI: 10.1016/j.cyto.2005.10.002]

174 Sanders PM, Russell ST, Tisdale MJ. Angiotensin II directly induces muscle protein catabolism through the ubiquitin-proteasome proteolytic pathway and may play a role in cancer cachexia. *British journal of cancer* 2005; **93**(4): 425-434 [PMID: 16052213 PMCID: 3217221 DOI: 10.1038/sj.bjc.6602725]

175 Springer J, Tschirner A, Haghikia A, von Haehling S, Lal H, Grzesiak A, Kaschina E, Palus S, Potsch M, von Websky K, Hocher B, Latouche C, Jaisser F, Morawietz L, Coats AJ, Beadle J, Argiles JM, Thum T, Foldes G, Doehner W, Hilfiker-Kleiner D, Force T, Anker SD. Prevention of liver cancer cachexia-induced cardiac wasting and heart failure. *European heart journal* 2014; **35**(14): 932-941 [PMID: 23990596 PMCID: 3977133 DOI: 10.1093/eurheartj/eht302]

176 de Gramont A, Chibaudel B, Larsen AK, Tournigand C, Andre T. The evolution of adjuvant therapy in the treatment of early-stage colon cancer. *Clinical colorectal cancer* 2011; **10**(4): 218-226 [PMID: 22122893 DOI: 10.1016/j.clcc.2011.10.001]

177 Mantovani G, Maccio A, Madeddu C, Gramignano G, Lusso MR, Serpe R, Massa E, Astara G, Deiana L. A phase II study with antioxidants, both in the diet and supplemented, pharmaconutritional support, progestagen, and anti-cyclooxygenase-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2006; **15**(5): 1030-1034 [PMID: 16702388 DOI: 10.1158/1055-9965.EPI-05-0538]

178 Kumar NB, Kazi A, Smith T, Crocker T, Yu D, Reich RR, Reddy K, Hastings S, Exterman M, Balducci L, Dalton K, Bepler G. Cancer cachexia: traditional therapies and novel molecular mechanism-based approaches to treatment. *Current treatment options in oncology* 2010; **11**(3-4): 107-117 [PMID: 21128029 PMCID: 3016925 DOI: 10.1007/s11864-010-0127-z]

179 Couch M, Lai V, Cannon T, Guttridge D, Zanation A, George J, Hayes DN, Zeisel S, Shores C. Cancer cachexia syndrome in head and neck cancer patients: part I. Diagnosis, impact on quality of life and survival, and treatment. *Head & neck* 2007; **29**(4): 401-411 [PMID: 17285641 DOI: 10.1002/hed.20447]

180 Lundholm K, Daneryd P, Bosaeus I, Korner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: Effects on survival, metabolism, and function. *Cancer* 2004; **100**(9): 1967-1977 [PMID: 15112279 DOI: 10.1002/cncr.20160]

181 Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *Journal of the National Cancer Institute* 2012; **104**(5): 371-385 [PMID: 22345712 DOI: 10.1093/jnci/djr556]

182 Lenk K, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *Journal of cachexia, sarcopenia and muscle* 2010; **1**(1): 9-21 [PMID: 21475693 PMCID: 3060644 DOI: 10.1007/s13539-010-0007-1]

183 Toledo M, Busquets S, Sirisi S, Serpe R, Orpi M, Coutinho J, Martinez R, Lopez-Soriano FJ, Argiles JM. Cancer cachexia: physical activity and muscle force in tumour-bearing rats. *Oncology reports* 2011; **25**(1): 189-193 [PMID: 21109976]

184 Baltgalvis KA, Berger FG, Pena MM, Davis JM, White JP, Carson JA. Muscle wasting and interleukin-6-induced atrogin-I expression in the cachectic Apc ( Min/+ ) mouse. *Pflugers Archiv : European journal of physiology* 2009; **457**(5): 989-1001 [PMID: 18712412 PMCID: 2867110 DOI: 10.1007/s00424-008-0574-6]

185 Weber MA, Krakowski-Roosen H, Schroder L, Kinscherf R, Krix M, Kopp-Schneider A, Essig M, Bachert P, Kauczor HU, Hildebrandt W. Morphology, metabolism, microcirculation, and strength of skeletal muscles in cancer-related cachexia. *Acta Oncol* 2009; **48**(1): 116-124 [PMID: 18607877 DOI: 10.1080/02841860802130001]

186 Aulino P, Berardi E, Cardillo VM, Rizzuto E, Perniconi B, Ramina C, Padula F, Spugnini EP, Baldi A, Faiola F, Adamo S, Coletti D. Molecular, cellular and physiological characterization of the cancer cachexia-inducing C26 colon carcinoma in mouse. *BMC cancer* 2010; **10**: 363 [PMID: 20615237 PMCID: 2912868 DOI: 10.1186/1471-2407-10-363]

187 Radbruch L, Elsner F, Trottenberg P, Strasser F, Fearon K. Clinical practice guidelines on cancer cachexia in advanced cancer patients. Department of Palliative Medicinen/European Palliative Care Research Collaborative. Aachen, 2010.

188 Ardies CM. Exercise, cachexia, and cancer therapy: a molecular rationale. *Nutrition and cancer* 2002; **42**(2): 143-157 [PMID: 12416253 DOI: 10.1207/S15327914NC422\_1]

189 al-Majid S, McCarthy DO. Cancer-induced fatigue and skeletal muscle wasting: the role of exercise. *Biological research for nursing* 2001; **2**(3): 186-197 [PMID: 11547540]

190 Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, Oredalen E, Frantzen TL, Lesteberg I, Amundsen L, Hjermstad MJ, Haugen DF, Paulsen O, Kaasa S. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. *The oncologist* 2011; **16**(11): 1649-1657 [PMID: 21948693 PMCID: 3233301 DOI: 10.1634/theoncologist.2011-0133]

191 Argiles JM, Busquets S, Lopez-Soriano FJ, Costelli P, Penna F. Are there any benefits of exercise training in cancer cachexia? *Journal of cachexia, sarcopenia and muscle* 2012; **3**(2): 73-76 [PMID: 22565649 PMCID: 3374018 DOI: 10.1007/s13539-012-0067-5]

192 Aagaard P. Making muscles "stronger": exercise, nutrition, drugs. *Journal of musculoskeletal & neuronal interactions* 2004; **4**(2): 165-174 [PMID: 15615119]

193 Bossola M, Muscaritoli M, Costelli P, Grieco G, Bonelli G, Pacelli F, Fanelli FR, Doglietto GB, Baccino FM. Increased muscle proteasome activity correlates with disease severity in gastric cancer patients. *Annals of surgery* 2003; **237**(3): 384-389 [PMID: ISI:000185834100014 DOI: Doi 10.1097/00000658-200303000-00013]