3-26-2021

# Metabolism and Oncology: the Role of Nutrition in Improving Cancer Outcomes

Michael A. Chapek
*Portland State University*

# Metabolism and Oncology: The Role of Nutrition in Improving Cancer Outcomes

by

Michael A. Chapek

An undergraduate honors thesis submitted in partial fulfillment of

the requirements for the degree of Bachelor of Arts in

Public Health Studies: Pre-Clinical Health Sciences

and University Honors

Thesis Advisor

Robert G. Martindale MD, PhD

**Portland State University**

**2021**

## Dedication

This thesis is dedicated to my grandmother and grandfather, Patty and Jim Kimber, who both lost their battles with COVID-19 in August of 2020. They gave me a place to live, study and be encouraged during my time at Portland State. The successful completion of my undergraduate education and my subsequent acceptance to medical school were made possible by their unwavering support. My gratitude to them cannot be overstated.

## Abstract

Despite significant advances in oncologic treatment, underlying cancer-associated metabolic derangements and nutritional needs remain largely neglected in cancer care. Cancer cachexia and protective metabolic changes exhibited by cancerous cells continue to pose formidable barriers to improving therapeutic outcomes and quality of life for patients. Cancer has traditionally been viewed as a proliferative disease caused by genetic mutations, but newer perspectives suggest that it is primarily a metabolic disease. The present paper discusses the etiology of cachexia and sarcopenia, and nutritional interventions that can be offered to patients suffering from these wasting disorders. The role of inflammation in cancer and the methods for preventing and resolving it with nutrition are also explored. Ultimately, a number of nutritional recommendations aimed at overcoming cachexia, resolving inflammation and improving cancer outcomes are provided based on a review of the current literature.

**The Warburg Effect: An Old Concept with Renewed Interest**

It has long been known that cancer cells have distinct metabolic behaviors that promote their growth and facilitate proliferation. Perhaps the most famous metabolic change is the Warburg Effect, a phenomenon identified roughly a century ago, wherein proliferating cells exhibit an impressive increase in glucose uptake and lactate production, even in aerobic conditions.[1] The Warburg Effect has a number of proposed functions, including more rapid ATP synthesis to support the biosynthetic needs of proliferation; acidification of the tumor microenvironment via lactate secretion to disrupt the immune response; and altered cell signaling with neighboring tumor cells to promote metastasis.[2,3]

Around the time of Warburg's original work, other investigators attempted to exploit the metabolic changes of tumors cells with some success in animal models.[4] Unfortunately, due to disparate study outcomes in large human trials and challenges in translation from basic science to clinical practice, metabolism and nutrition became largely neglected in cancer care.[5,6] Despite extensive investigation into the metabolic derangements exhibited by cancer cells, cancer has primarily been viewed as a disease of proliferation that is initiated and maintained by genetic mutations.[7] That notion has rapidly changed. A growing body of research suggests that cancer should be viewed as a metabolic disease.[8-11] Further, dysregulated metabolism once again appears to be a promising therapeutic target that can help address cancer-associated inflammation and even genomic and transcriptional changes associated with cancer.[12] With the resurgence of this perspective, there has been renewed interest in metabolic manipulation to improve cancer outcomes. In this paper, the current status of nutritional therapy with respect to managing cancer-associated cachexia and improving outcomes for cancer patients is explored.

**Cancer Cachexia and Sarcopenia**

Cachexia is a very common feature of advanced cancer, defined as an insidious, unintentional loss of skeletal muscle mass (as well as potential loss of fat mass) that persists despite conventional nutritional interventions.[13,14] Many patients, even at their first visit with a medical oncologist, already have anorexia, malnutrition and weight loss.[14] In the setting of advanced cancers of many types, cachexia bears the risk of diminished responsiveness to chemotherapy and radiotherapy, worse quality of life and reduced duration of survival, making it a critical target for nutritional therapy.[15-17] Assuming that cancer cachexia is a product of simple nutrient deficiency, it would be reasonable to believe that protein and calorie supplementation would improve outcomes for all patients. In reality, cachexia is a complex, multi-factorial syndrome that cannot be fully explained by decreased nutrient intake alone. Although protein and calorie supplementation does generally result in some weight gain, it does not always translate to improved outcomes for patients.[18]

A wide variety of metabolic changes are partially to blame for cancer cachexia. Tumor growth incites inflammation and a rise in proinflammatory cytokines. These cytokines upregulate adipose triglyceride lipase activity, resulting in an increase in plasma free fatty acids.[19] Concurrently, enhanced lipolytic effect from catecholamines, a phenomenon observed in cachectic cancer patients, causes further increase in enzymatic lipolytic activity.[20] The consequent loss of fat mass from these processes appears to be an early step in the initiation of cachexia.[21] Surprisingly, the resultant increase in serum free fatty acids after lipolysis seems to have a key function in muscle catabolism. Abnormal crosstalk between muscle tissue and fatty tissue via circulating free fatty acids is a critical part of cachexia during chronic inflammation.[19] Animal studies suggest that this increase in free fatty acids corresponds to muscle catabolism,

ultimately resulting in sarcopenia, or loss of skeletal muscle mass.[22] These catabolic effects seen as a result of chronic inflammation can be further exacerbated by lipolysis and proteolysis related to chemotherapy.[23]

As patients lose functionality and mobility—due to treatment, progressed disease, or other disability—they are at greater risk for immobilization-induced muscle atrophy. In immobilized populations, decreased protein turnover and anabolic resistance are major underlying factors that prevent muscle maintenance and growth.[24] Immobilization combined with the various metabolic changes associated with cancer all support the initiation and progression of cachexia and sarcopenia.

*Cachexia and Sarcopenia Diagnosis: Identifying Occult Disease*

Despite being a common feature of progressed cancer, cachexia is underdiagnosed and often goes untreated.[25] Part of the challenge is that assessing cachexia clinically—based solely on changes in body weight—offers an incomplete view of nutritional status and prognosis. A much stronger indicator of poor prognosis is cachexia with sarcopenia, which is strongly predictive of treatment toxicity, postoperative complications after tumor resections, and shorter overall survival.[26,27] In the age of the obesity epidemic, many obese patients may not be identified as having sarcopenia at the time of diagnosis despite potentially presenting with significant underlying skeletal muscle loss. Cross-sectional imaging modalities—such as CT and MRI—have traditionally been used in oncology for tumor visualization and treatment planning, but these imaging modalities can also evaluate for skeletal muscle wasting before a patient is frankly sarcopenic.[13] These new uses of imaging are revealing that cachexia and sarcopenia develop in cancer patients much earlier than previously assumed. A growing number of studies

show a strong relationship between CT-proven sarcopenia and disease outcomes not only in a variety of cancers, but in other serious illnesses, as well.[28-32] Early identification of occult sarcopenia is particularly valuable in the obese population, as sarcopenic obesity is a strong predictor of survival, independent of age, sex and functional status.[33,34]

*Addressing Cachexia and Sarcopenia*

Once a patient has been identified as cachectic, the severity of their cachexia must be gauged. Patients with cachexia exist on a spectrum that includes pre-cachexia, cachexia and refractory cachexia; these stages are defined based on clinical presentation, the degree of weight loss and the presence of sarcopenia.[35] The stage of cachexia should be used to guide discussions about the goals of care with the patient. Those deemed to have refractory cachexia are very unlikely to realize any benefits from nutritional therapy, so palliative measures and comfort for the patient and their family should be the primary focus.[35,36] However, if cachexia is identified in either of the first two stages, nutrition may be beneficial. Pre-cachectic patients often present with anorexia and modest weight loss, if any. They should be assessed for underlying symptomology causing anorexia (constipation, pain, nausea from chemotherapy, etc.) followed by appropriate treatment of symptoms to encourage intake. Food intake—especially protein intake—should be gauged regularly. A serum C-reactive protein (CRP) may be drawn to evaluate for systemic inflammation as a possible driver of catabolism, but it is important to note that cachexia and associated inflammation can be present without an observed CRP elevation.[37] Several molecules have been explored as biomarkers for cachexia, but their utility has not been confirmed in large prospective studies, and many of the test are not readily available to clinicians.[38]

Patients who have progressed to the cachectic stage should undergo a thorough evaluation of the causes of their cachexia and multimodal management should be initiated. Nutrition and lifestyle interventions in these patients should focus on maintaining muscle mass. Generally speaking, mechanistic data on critically ill patients supports supplementation of protein or amino acids, be it enterally or parenterally.[39-46] Aerobic and resistance exercises are a necessary compliment to increased protein intake as these activities promote anabolism and maintain skeletal muscle mass.[47-49] Although many of their mechanisms are incompletely understood, some appetite stimulants are also being examined for their role in addressing cachexia. Megestrol acetate, corticosteroids and anamorelin, a pharmaceutical ghrelin agonist, have been shown to improve caloric intake and weight stability, but they also come with a host of side-effects and are not yet widely used in the clinical setting.[50] Cannabinoids are also being investigated for their role as antiemetics and appetite stimulants.[51] However, most appetite stimulants have yet to receive robust support from the literature.

In cancer patients, it is important to understand the factors that contribute to the anabolic resistance observed in cancer. Systemic availability of amino acids and the route by which they are delivered both contribute to anabolic resistance. Ideally, patients should receive amino acid supplementation via enteral feeding, as it results in more effective utilization of amino acids than parenteral feeding.[52] Branched-chain amino acids, especially leucine, prevent muscle breakdown by promoting protein synthesis.[53] Supplementation of leucine and leucine metabolites, such as hydroxymethylbutyrate, have been shown to promote maintenance of muscle mass and growth.[24] Similarly, supplementation of glutamine, carnitine, creatine and vitamin D with whey protein also support muscle mass growth and muscle function in the sarcopenic population.[54] Additionally, supplementation of arginine and nucleotides has been shown to bolster immunity

in surgical and radiation patients with cancer.[47] Complementing this supplementation with resistance exercises is also critical for promoting maintenance of muscle mass and preventing atrophy from disuse.[55]

## Inflammation and Cancer

Inflammation is a key part of the etiology of many common diseases, ranging from diabetes and obesity to autoimmune diseases, and even cancer. Although the incidence of infectious diseases has steadily decreased over the last half a century, there has been a rise in diseases of inflammatory origin, such as allergic and autoimmune diseases.[56,57] Many infections are associated with the onset of cancer. Some of the most famous associations include *Helicobacter pylori* (and other gastric microbes) and gastric cancer, hepatitis B or hepatitis C and liver cancer, and human papillomavirus and cervical cancer, among many others.[58-61]. *H. pylori*, a class one carcinogen according to the World Health Organization, infects at least half of the world's population, with wide variations in infection rates between high-income countries and low- and middle-income countries.[62,63] Infection-associated cancers bear a significant burden worldwide, as it is estimated that between 20% and 40% of all cancers are related to chronic infection and the associated inflammation.[64]

### *Inflammation as a Carcinogenic Process*

While infection is a key player in many cancers, the prolonged increase in diseases of inflammatory origin cannot be explained by infection alone. Obesity in the setting of metabolic disease poses serious risk for cancer and has been shown to impact the occurrence and growth of a variety of cancers.[65] This is mainly due to the proinflammatory state incited by obesity and

metabolic disease. Inflammation associated with obesity is marked by changes from adipose-tissue macrophages to the M1 'proinflammatory' phenotype from the M2 anti-inflammatory phenotype; increased creation of many proinflammatory cytokines; elevated glucose and free fatty acid levels; and even dysbiosis of colonic microbiota resulting in greater prevalence of bacterial species that secrete pro-carcinogenic metabolites.[66] Recent mitochondrial investigation has also implicated mitochondrial dysfunction in the facilitation of chronic inflammation, known to promote certain cancers.[67] Indeed, inflammation seems to influence virtually every step of the neoplastic process by increasing DNA damage, decreasing sensitivity to growth inhibitors, promoting tissue evasion and metastasis, sustaining angiogenesis and promoting evasion of apoptosis and senescence.[63,64,68,69]

*Putting out the Fire: Oil Sources*

It is acknowledged that successfully treating cancer and associated cachexia will require a multifaceted approach that addresses energy intake, activity level and inflammation. Because manipulation of energy intake has not been consistently successful in cancer treatment and manipulation of activity has not been studied as thoroughly, inflammation is the current major focus for intervention.[13] Various oil sources have been investigated for their roles as energy sources and have been compared based on their proinflammatory characteristics. Studies comparing oil sources in patients requiring parenteral nutrition (PN) have made it clear that some oil sources vary tremendously in their incitation of inflammation and their promotion of carcinogenesis.[70,71] Standard intravenous lipid emulsions in the United States generally contain soybean oil, but there is a growing consensus that other oil sources may confer greater benefit. Transitioning from a soybean oil emulsion to a mixed lipid emulsion containing fish oil has

shown to attenuate systemic inflammation and bolster immunity.[72] The use of polyunsaturated fatty acids (PUFAs), such as those found in fish oil, is supported both by clinical and biochemical investigation, which show decreased inflammation and improved outcomes in some cancers.[47, 73] Other studies have shown that medium-chain triglycerides, such as those from purified coconut or palm kernel oil, are an excellent source of energy that is not only less inflammatory than soybean oil, but that promotes ketogenesis and protein sparing, and is resistant to peroxidation.[74] Many nutrients and biomolecules in foods also have significant immunologic activity. Among these are glutamine, arginine and nucleotides, which have strong anti-inflammatory, immunomodulatory and cytoprotective effects in various organs.[47, 75]

Along with influencing systemic inflammation, marine-derived oil sources also effect tumors and their growth directly. This is primarily due to the fact that marine-derived oil sources contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two long-chain ω-3 PUFAs. Tumors of patients provided with marine-derived oil containing EPA and DHA exhibit decreased cell proliferation, enhanced apoptosis, and limited tumor angiogenesis.[76,77] EPA and DHA also bolster the effects of chemotherapy and have been shown to enhance tumor toxicity to antineoplastic drugs while protecting non-tumor tissue.[78,79] Although there are many promising studies exploring the influence of marine-based oil sources on cancer, the literature is quite confusing with many studies showing conflicting results. For instance, only an equivocal relationship exists between intake of marine-derived fatty acids and risk of prostate cancer.[80] Some of the most encouraging data is in the colorectal literature. A meta-analysis of human studies that examined 22 prospective cohort studies and 19 case-controlled trials concluded that consumption of fish decreased the risk of colorectal cancer by 12%.[81] Further, proinflammatory

acids, such as saturated fatty acids, have a high association with increased risk of colorectal cancer.[82]

*Palliative Properties of Marine-Derived Oils*

In addition to decreasing inflammation and strengthening the response to cancer therapy, marine-derived fatty acids can be palliative. Cancer patients face a host of symptoms that impair their functionality and decrease quality of life. Gastrointestinal symptoms are among the most common complaints of patients receiving chemotherapy, particularly those being treated for gastrointestinal cancers. De Quadros Camargo and colleagues carried out a randomized, placebo-controlled, triple blind clinical trial examining treatment outcomes, adverse events, side-effects and functionality of patients receiving fish oil and placebo. The fish oil group had less gastrointestinal symptoms and better performance scores compared to the placebo group, but there was no difference in lipid peroxidation or adverse events between groups.[83]

While many studies on fish oil use are promising, it is important to keep in mind that much of the data on outcomes is conflicting and inconsistent. A randomized, placebo-controlled trial of 25,871 individuals receiving either fish oil supplementation or placebo demonstrated no influence of fish oil on cancer or cardiovascular disease prevention.[84] Some meta-analyses also show that PUFAs have no effect on overall cancer diagnosis or cancer death, and that it may even raise the risk of cancer diagnosis for some specific diseases.[85] It is unclear if fish oil offers any protection against loss of muscle mass and function.[86] Further investigation is warranted to elucidate the role of fish oil in preventing cancer and bolstering cancer treatment, but it does appear to offer at least some palliative benefit in some settings.

*Resolving Inflammation*

Inflammation consists of two phases—initiation and resolution—which are orchestrated by complex interactions between cells and signaling molecules.[87] Although much discussion of inflammation centers around preventing the initiation phase, it is equally important to understand and address the resolution of inflammation. Among the most critical chemical signals for resolving inflammation are specialized pro-resolving mediators (SPMs), which are a group of biologic mediators that consist of resolvins, protectins and maresins.[88] These families of molecules intervene in instances of both acute and chronic inflammation to promote resolution and ultimately encourage tissue repair and healing. There is a close relationship between EPA, DHA and SPMs wherein enzymatic lipoxygenase activity on ω-3 or ω-6 PUFAs gives rise to SPMs.[89] PUFAs and SPMs have a number of characteristics in common, as they are both naturally occurring, synthesized endogenously in humans and possess anti-inflammatory properties. However, only SPMs have the ability to directly orchestrate resolution of inflammation. Clinical studies have shown that fish oil supplementation does result in increased ω-3 index and increased plasma levels of downstream mediators, such as SPMs.[90]

SPMs not only modulate inflammation, but also help combat disease. Their evolutionary conservation across a wide variety of species suggests that they are indispensable immune molecules.[91] Greater concentrations of various SPMs have been associated with decreased mortality in septic patients, decreased rates of surgical infections and even altered angiogenesis and tumor microenvironment.[91-93] SPMs are implicated in various steps of neoplastic progression, especially inflammation and angiogenesis. Cancer cells treated with SPMs, such as Resolvin D1 and Lipoxin B4, exhibit significantly diminished angiogenic potential. Additionally, supplementation of ω-3 and ω-6 fatty acids promotes endogenous production of SPMs.[89]

*Promoting Endogenous Production of Specialized Pro-resolving Mediators*

Promotion of endogenous production of SPMs that facilitate effective clearance of tumor debris is an emerging therapeutic target that can be promoted both nutritionally and pharmacologically. Observational data suggesting a protective effect of aspirin against cancer has garnered interest in the mechanism by which this protection occurs.[94] Biochemical literature has shown that aspirin promotes endogenous production of aspirin-triggered SPMs, including resolvins and lipoxins. These aspirin-triggered SPMs cause greater macrophage phagocytosis of tumor cells and debris while counter-regulating a number of proinflammatory molecules secreted by macrophages.[95] These changes in the immediate vicinity of the tumor and their protection against cancer highlight the importance of the tumor microenvironment. Although cancer therapy reduces disease burden by killing tumors, it simultaneously leaves tumor debris in the area of the tumor which promotes inflammation and tumor recurrence. New research has shown that debris-stimulated tumors were inhibited by SPMs, such as resolvins D1, D2 and D3.[88] Furthermore, pre-operative stimulation of resolvins via ketorolac injection in mouse models was shown to prevent dormancy escape, micrometastasis and later tumor recurrence caused by chemotherapy and surgery.[96]

**Emerging Nutrition Therapies: Fact or Fad?**

*Whole Grains*

A variety of nutritional therapies have gain traction both in the lay media and in the scientific literature. Among the most well-supported nutritional cancer prevention methods is increased intake of whole grains. As little as three servings per day of whole grains has been shown to decrease all-cause mortality, including cardiac disease, stroke, type 2 diabetes and

cancer.[97,98] A prospective cohort study following 786,076 patients also showed decreased all-cause mortality associated with whole grains.[99] A variety of mechanisms are thought to contribute to the anti-cancer properties of whole grains, including their bioactive phytochemicals known to reduce cancer risk; their role as a source of dietary fiber that can be fermented to make short-chain fatty acids, such as butyrate; their association with reduced risk of obesity and metabolic disease; and their antioxidant and anti-inflammatory properties.[100,101]

*Prebiotics and Probiotics*

The host microbiome plays a vital role in modulating the inflammatory state of the colon. Probiotics have been employed to address treatment-associated symptoms and, in some cancers, to promote prevention. Various mechanisms contribute to the anticarcinogenic effect of probiotics, including production of anti-inflammatory molecules such as short-chain fatty acids, degradation of carcinogens in the colonic lumen, immune modulation and bolstering of the intestinal barrier through promotion of gut homeostasis.[102,103] In patients with colorectal cancer, use of probiotics improves immunity and decreases gastrointestinal complaints while reducing tumor formation, proliferation, growth and metastasis.[104-106] Other cancers, such as pancreatic cancer, are thought to partially arise due to differential increases in select pathogenic bacteria which activate immune receptors that promote inflammation and spur on cancer.[107,108] There is also evidence showing that probiotics decrease inflammation and cachexia while preventing muscle loss in mouse models.[109] Probiotics may also be a potential tool for controlling cellular injury during adjuvant chemoradiation, but review of the literature reveals very mixed results.[110,111]

*Ketogenic Diet and Fasting*

Among the most popular emerging nutritional therapies are intermittent fasting and the ketogenic diet, the ladder of which has been explored for its role in weight loss, epilepsy treatment, diabetes management and cancer care.[112] The ketogenic diet, which is a low carb, high fat diet, is based on the idea that the absence of glucose will force the cell to rely on fatty acid oxidation, rather than glycolysis, for energy.[113] Given that hyperglycemia and impaired insulin sensitivity are generally associated with worse cancer outcomes, a low-carb diet is an effective method for decreasing blood glucose.[114] In some cancers, particularly gliomas, the ketogenic diet has offered promising results when used concurrently with radiation therapy.[11,115] In animal models, the ketogenic diet with hyperbaric oxygen treatment decreased the size of certain implanted metastatic tumors.[116] However, the benefits of the ketogenic diet are not realized in all cancers, and further investigation is needed to better understand in what settings the ketogenic diet should be recommended.[117,118] Another dietary measure that takes advantage of altered tumor metabolism is intermittent fasting, which has been shown to slow tumor growth and enhance tumor sensitivity to chemotherapy.[119] Given the significant change in lifestyle and the many unanswered questions about ketogenic diets and intermittent fasting, patients pursuing either should be thoroughly counseled by a physician to achieve the best compliance, and understand the risks, benefits, limitations and unknowns.[120]

**Exercise and Cancer**

Physical activity is a key compliment to optimal nutrition in cancer patients. Generally speaking, clinical, functional, and in certain groups, survival outcomes improve with exercise.[121-122] Studies using rat models have demonstrated that voluntary running inhibits tumor growth

through increased vascularization and blood perfusion, improved immune function, altered tumor metabolism and muscle-to-tumor crosstalk.[123-125] In humans, high intensity exercise has been shown to reduce colon cancer cell growth and colon cancer mortality, although the precise mechanism is unclear and the effects appear to be transient.[126] Conversely, sedentary lifestyle seems to increase risk of cancer mortality.[127] Part of the benefit of exercise is likely attributable to its role in controlling inflammation by decreasing fat mass.[128] Preoperative exercise may also be beneficial to surgical oncology patients, as it is associated with a quicker functional recovery, but these outcomes are likely not specific to surgical oncology.[129,130] Further research is needed to explore roles and mechanisms of exercise in improving cancer-specific outcomes.

**Takeaways: How to Guide Patients**

Overcoming cachexia and improving cancer outcomes are formidable challenges that require a multimodal approach. As early as possible, patients should be evaluated for underlying cachexia and sarcopenia, likely with the assistance of cross-sectional imaging to best assess muscle atrophy.[13] Once the stage of cachexia has been identified, a conversation about goals of care must take place. Patients identified as pre-cachectic or cachectic should begin targeted multimodal therapy, focused on combatting catabolism and inflammation through increased protein intake, incorporation of anti-inflammatory foods and supplements (ideally via enteral route), and correction of symptoms causing anorexia.[47] Increased protein, including supplementation of leucine and leucine metabolites, should be done in combination with aerobic exercises and resistance exercises to maintain muscle mass.[24] In patients with refractory cachexia, the focus should be on palliation and symptom management, with the goal of bringing comfort to the patient and their family.[35] For patients complaining of gastrointestinal symptoms,

good evidence exists to suggest that marine-derived oils and probiotics as well as whole grains can significantly alleviate their symptoms.[83]

Much of the role of nutrition in cancer centers around addressing inflammation. A less inflammatory oil source should be chosen wisely. Marine-derived oils containing PUFAs, such as EPA and DHA, are ideal oil sources because of their inherent anti-inflammatory properties, and their close relationships with SPMs.[76, 77, 89] Surgical oncology patients and patients receiving chemotherapy or radiotherapy are most likely to reap the benefits of fish oil such as decreased micrometastases and less chance of future recurrence from dormancy escape.[96, 131] Medium-chain triglycerides, such as those in purified coconut oil or palm kernel oil, are also valid oil sources as they are less inflammatory, enhance ketogenesis and promote protein sparing.[74] In certain patient populations, specifically patients with gliomas, there may be benefit in recommending the ketogenic diet, but this recommendation is not substantiated by robust bodies of research in many other cancers.[115, 117]

One vital responsibility of the clinician is to counsel patients on their options and support them as they commit to the demanding lifestyle changes of cancer care. A team-based approach, involving physicians, dieticians, patients and their families is recommended to facilitate successful adoption of individualized diet modification and exercise.[132,133] By understanding the role of nutrition, individualizing nutrition plans and counseling patients thoroughly, practitioners have the opportunity to combat cancer-cachexia and improve overall cancer outcomes.

**References**


1. Potter M, Newport E, Morten KJ. The Warburg effect: 80 years on. *Biochemical Society Transactions*. 2016;44(5):1499-1505.
2. Liberti MV, Locasale JW. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends in Biochemical Sciences*. 2016;41(3):211-218.
3. Danhier P, Bański P, Payen VL, et al. Cancer metabolism in space and time: Beyond the Warburg effect. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*. 2017;1858(8):556-572.
4. van Ness van Alstyne E, Beebe SP. The effect of non-carbohydrate diet upon the growth of transplantable sarcoma in rats. *J Med Res*. 1913;29(2):217-232.
5. Caccialanza R, De Lorenzo F, Gianotti L, et al. Nutritional support for cancer patients: still a neglected right? *Support Care Cancer*. 2017;25(10):3001-3004.
6. Di Sebastiano KM, Murthy G, Campbell KL, et al. Nutrition and Cancer Prevention: Why is the Evidence Lost in Translation? *Advances in Nutrition*. 2019;10(3):410-418.
7. Hanahan D, Weinberg RA. The Hallmarks of Cancer. *Cell*. 2000;100(1):57-70.
8. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. *Cell*. 2011;144(5):646-674.
9. Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. *Carcinogenesis*. 2014;35(3):515-527.
10. Coller HA. Is Cancer a Metabolic Disease? *The American Journal of Pathology*. 2014;184(1):4-17.
11. Poff A, Koutnik AP, Egan KM, et al. Targeting the Warburg effect for cancer treatment: Ketogenic diets for management of glioma. *Seminars in Cancer Biology*. 2019;56:135-148.

12. Nanda C, Venkateswaran SV, Patani N, Yuneva M. Defining a metabolic landscape of tumours: genome meets metabolism. *Br J Cancer*. 2020;122(2):136-149.
13. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol*. 2013;10:90-99.
14. Muscaritoli M, Lucia S, et al. Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. *Oncotarget*. 2017;8(45):79884-79896.
15. Sadeghi M, Keshavarz-Fathi M, Baracos V, Arends J, Mahmoudi M, Rezaei N. Cancer cachexia: Diagnosis, assessment, and treatment. *Critical Reviews in Oncology/Hematology*. 2018;127:91-104.16.
16. Lu Z, Yang L, Yu J, et al. Change of Body Weight and Macrophage Inhibitory Cytokine-1 during Chemotherapy in Advanced Gastric Cancer: What Is Their Clinical Significance? Chen Y-J, ed. *PLoS ONE*. 2014;9(2):1-9.
17. Kwon M, Kim RB, Roh J-L, et al. Prevalence and clinical significance of cancer cachexia based on time from treatment in advanced-stage head and neck squamous cell carcinoma: Cancer cachexia in advanced head and neck cancer. *Head Neck*. 2017;39(4):716-723.
18. Nasrah R, Kanbalian M, Van Der Borch C, Swinton N, Wing S, Jagoe RT. Defining the role of dietary intake in determining weight change in patients with cancer cachexia. *Clinical Nutrition*. 2018;37(1):235-241.
19. Fearon KCH. Cancer Cachexia and Fat–Muscle Physiology. *N Engl J Med*. 2011;365(6):565-567.
20. Agustsson T, Rydén M, Hoffstedt J, et al. Mechanism of Increased Lipolysis in Cancer Cachexia. *Cancer Res*. 2007;67(11):5531-5537.
21. Arner P. Lipases in Cachexia. *Science.* 2011;33:163-164.

22. Das SK, Eder S, Schauer S, et al. Adipose Triglyceride Lipase Contributes to Cancer-Associated Cachexia. *Science*. 2011;333:233-238.
23. Schiessel DL, Baracos VE. Barriers to cancer nutrition therapy: excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. *Proceedings of the Nutrition Society*. 2018;77:394-402.
24. Magne H, Savary-Auzeloux I, Rémond D, Dardevet D. Nutritional strategies to counteract muscle atrophy caused by disuse and to improve recovery. *Nutr Res Rev*. 2013;26(2):149-165.
25. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers*. 2018;4(1):1-18.
26. Laviano A, Di Lazzaro L, Koverech A. Nutrition support and clinical outcome in advanced cancer patients. *Proc Nutr Soc*. 2018;77(4):388-393.
27. Martin L, Birdsell L, MacDonald N, et al. Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index. *JCO*. 2013;31(12):1539-1547.
28. Peng P, Hyder O, Firoozmand A, et al. Impact of Sarcopenia on Outcomes Following Resection of Pancreatic Adenocarcinoma. *J Gastrointest Surg*. 2012;16(8):1478-1486.
29. Moisey LL, Mourtzakis M, Cotton BA, et al. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. *Crit Care*. 2013;17(5):R206.
30. Kirk PS, Friedman JF, Cron DC, et al. One-year postoperative resource utilization in sarcopenic patients. *Journal of Surgical Research*. 2015;199(1):51-55.

31. Okumura S, Kaido T, Hamaguchi Y, et al. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. *Surgery*. 2015;157(6):1088-1098.
32. Prado CM, Purcell SA, Alish C, et al. Implications of low muscle mass across the continuum of care: a narrative review. *Annals of Medicine*. 2018;50(8):675-693.
33. Deutz NEP, Ashurst I, Ballesteros MD, et al. The Underappreciated Role of Low Muscle Mass in the Management of Malnutrition. *Journal of the American Medical Directors Association*. 2019;20(1):22-27.
34. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The Lancet Oncology*. 2008;9(7):629-635.
35. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *The Lancet Oncology*. 2011;12(5):489-495.
36. Liposits G, Orrevall Y, Kaasa S, Österlund P, Cederholm T. Nutrition in Cancer Care: A Brief, Practical Guide With a Focus on Clinical Practice. *JCO Oncology Practice.* 2020;1-8.
37. Penafuerte CA, Gagnon B, Sirois J, Murphy J, MacDonald N, Tremblay ML. Identification of neutrophil-derived proteases and angiotensin II as biomarkers of cancer cachexia. *Br J Cancer*. 2016;114(6):680-687.
38. Loumaye A, Thissen JP. Biomarkers of cancer cachexia. *Clinical Biochemistry*. 2017;50(18):1281-1288.
39. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. *Crit Care*. 2014;18(6):701.

40. Berg A, Rooyackers O, Bellander B-M, Wernerman J. Whole body protein kinetics during hypocaloric and normocaloric feeding in critically ill patients. *Crit Care*. 2013;17(4):R158.
41. Liebau F, Sundström M, van Loon LJ, Wernerman J, Rooyackers O. Short-term amino acid infusion improves protein balance in critically ill patients. *Crit Care*. 2015;19(1):106.
42. Liebau F, Wernerman J, van Loon LJ, Rooyackers O. Effect of initiating enteral protein feeding on whole-body protein turnover in critically ill patients. *The American Journal of Clinical Nutrition*. 2015;101(3):549-557.
43. Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. *Crit Care*. 2016;20(1):367.
44. Ferrie S, Allman-Farinelli M, Daley M, Smith K. Protein Requirements in the Critically Ill: A Randomized Controlled Trial Using Parenteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2016;40(6):795-805.
45. Sundström Rehal M, Liebau F, Tjäder I, Norberg Å, Rooyackers O, Wernerman J. A supplemental intravenous amino acid infusion sustains a positive protein balance for 24 hours in critically ill patients. *Crit Care*. 2017;21(1):298.
46. Weijs PJM, Mogensen KM, Rawn JD, Christopher KB. Protein Intake, Nutritional Status and Outcomes in ICU Survivors: A Single Center Cohort Study. *JCM*. 2019;8(1):43.
47. Arends J, Baracos V, Bertz H, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clinical Nutrition*. 2017;36(5):1187-1196.
48. von Haehling S. Casting the net broader to confirm our imaginations: the long road to treating wasting disorders: Editorial. *Journal of Cachexia, Sarcopenia and Muscle*. 2017;8(6):870-880.

49. Gould DW, Lahart I, Carmichael AR, Koutedakis Y, Metsios GS. Cancer cachexia prevention via physical exercise: molecular mechanisms. *J Cachexia Sarcopenia Muscle*. 2013;4(2):111-124.
50. Stubbins R, Bernicker EH, Quigley EMM. Cancer cachexia: a multifactoral disease that needs a multimodal approach. *Current Opinion in Gastroenterology*. 2020;36:141-146.
51. Wang J, Wang Y, Tong M, Pan H, Li D. New Prospect for Cancer Cachexia: Medical Cannabinoid. *J Cancer*. 2019;10(3):716-720.
52. Parent BA, Seaton M, Djukovic D, et al. Parenteral and enteral nutrition in surgical critical care: Plasma metabolomics demonstrates divergent effects on nitrogen, fatty-acid, ribonucleotide, and oxidative metabolism. *Journal of Trauma and Acute Care Surgery*. 2017;82(4):704-713.
53. Mirza KA, Pereira SL, Voss AC, Tisdale MJ. Comparison of the anticatabolic effects of leucine and Ca-β-hydroxy-β-methylbutyrate in experimental models of cancer cachexia. *Nutrition*. 2014;30(7-8):807-813.
54. Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. *Journal of Cachexia, Sarcopenia and Muscle*. 2020;11(2):366-380.
55. Sundström-Rehal M, Tardif N, Rooyackers O. Can exercise and nutrition stimulate muscle protein gain in the ICU patient? *Curr Opin Clin Nutr Metab Care*. 2019;22(2):146-151.
56. Bach J-F. The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases. *N Engl J Med*. 2002;347(12):911-920.
57. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. *Journal of Clinical Investigation*. 2018;128(7):2657-2669.

58. Moss SF. The Clinical Evidence Linking Helicobacter pylori to Gastric Cancer. *Cellular and Molecular Gastroenterology and Hepatology*. 2017;3(2):183-191.
59. Maucort-Boulch D, de Martel C, Franceschi S, Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide: Liver cancer attributable to hepatitis viruses worldwide. *Int J Cancer*. 2018;142(12):2471-2477.
60. Chan CK, Aimagambetova G, Ukybassova T, Kongrtay K, Azizan A. Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening, and Vaccination—Review of Current Perspectives. *Journal of Oncology*. 2019;2019:1-11.
61. Schulz C, Schütte K, Mayerle J, Malfertheiner P. The role of the gastric bacterial microbiome in gastric cancer: *Helicobacter pylori* and beyond. *Therap Adv Gastroenterol*. 2019;12:1-11.
62. Suerbaum S, Michetti P. Helicobacter pylori Infection. *The New England Journal of Medicine*. Published online 2002;347(15):1175-1185.
63. Morowitz MJ, Babrowski T, Carlisle EM, et al. The Human Microbiome and Surgical Disease. *Annals of Surgery*. 2011;253(6):1094-1101.
64. Kamp DW, Schacter E, Weitzman SA. Chronic inflammation and cancer; The role of the mitochondria. *Oncology.* 2011;25(5):400-410.
65. Hopkins BD, Goncalves MD, Cantley LC. Obesity and Cancer Mechanisms: Cancer Metabolism. *JCO*. 2016;34(35):4277-4283.
66. Zitvogel L, Pietrocola F, Kroemer G. Nutrition, inflammation and cancer. *Nat Immunol*. 2017;18(8):843-850.
67. Missiroli S, Genovese I, Perrone M, Vezzani B, Vitto VAM, Giorgi C. The Role of Mitochondria in Inflammation: From Cancer to Neurodegenerative Disorders. *JCM*. 2020;9(3):740.

68. Piotrowski I, Kulcenty K, Suchorska W. Interplay between inflammation and cancer. *Reports of Practical Oncology & Radiotherapy*. 2020;25(3):422-427.
69. Coussens LM, Werb Z. Inflammation and Cancer. *Nature*. 2002;420:860-867.
70. Vanek VW, Seidner DL, Allen P, et al. A.S.P.E.N. Position Paper: Clinical Role for Alternative Intravenous Fat Emulsions. *Nutr Clin Pract*. 2012;27(2):150-192.
71. Calder PC, Campoy C, Eilander A, et al. A systematic review of the effects of increasing arachidonic acid intake on PUFA status, metabolism and health-related outcomes in humans. *Br J Nutr*. 2019;121:1201-1214.
72. Martindale RG, Berlana D, Boullata JI, et al. Summary of Proceedings and Expert Consensus Statements From the International Summit "Lipids in Parenteral Nutrition." *JPEN J Parenter Enteral Nutr*. 2020;44:S7-S20.
73. Wei Y, Meng Y, Li N, Wang Q, Chen L. The effects of low-ratio n-6/n-3 PUFA on biomarkers of inflammation: a systematic review and meta-analysis. *Food Funct*. 2021;12(1):30-40.
74. Calder PC, Adolph M, Deutz NE, et al. Lipids in the intensive care unit: Recommendations from the ESPEN Expert Group. *Clinical Nutrition*. 2018;37(1):1-18.
75. Chitapanarux I, Traisathit P, Chitapanarux T, et al. Arginine, glutamine, and fish oil supplementation in cancer patients treated with concurrent chemoradiotherapy: A randomized control study. *Current Problems in Cancer*. 2020;44(1):1-10.
76. Szymczak M, Murray M, Petrovic N. Modulation of angiogenesis by ω-3 polyunsaturated fatty acids is mediated by cyclooxygenases. *Blood*. 2008;111(7):3514-3521.

77. Moloudizargari M, Mortaz E, Asghari MH, Adcock IM, Redegeld FA, Garssen J. Effects of the polyunsaturated fatty acids, EPA and DHA, on hematological malignancies: a systematic review. *Oncotarget*. 2018;9(14):11858-11875.
78. Shirai Y, Okugawa Y, Hishida A, et al. Fish oil-enriched nutrition combined with systemic chemotherapy for gastrointestinal cancer patients with cancer cachexia. *Sci Rep*. 2017;7(1):1-9.
79. Laviano A, Rossi Fanelli F. Toxicity in Chemotherapy — When Less Is More. *N Engl J Med*. 2012;366(24):2319-2320
80. Aucoin M, Cooley K, Knee C, et al. Fish-Derived Omega-3 Fatty Acids and Prostate Cancer: A Systematic Review. *Integr Cancer Ther*. 2017;16(1):32-62.
81. Wu S, Feng B, Li K, et al. Fish Consumption and Colorectal Cancer Risk in Humans: A Systematic Review and Meta-analysis. *The American Journal of Medicine*. 2012;125(6):551-559.
82. May-Wilson S, Sud A, Law PJ, et al. Pro-inflammatory fatty acid profile and colorectal cancer risk: A Mendelian randomisation analysis. *European Journal of Cancer*. 2017;84:228-238.
83. Camargo C de Q, Mocellin MC, Brunetta HS, et al. Fish oil decreases the severity of treatment-related adverse events in gastrointestinal cancer patients undergoing chemotherapy: A randomized, placebo-controlled, triple-blind clinical trial. *Clinical Nutrition ESPEN*. 2019;31:61-70.
84. Manson JE, Cook NR, Lee I-M, et al. Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med*. 2019;380(1):23-32.

85. Hanson S, Thorpe G, Winstanley L, Abdelhamid AS, Hooper L. Omega-3, omega-6 and total dietary polyunsaturated fat on cancer incidence: systematic review and meta-analysis of randomised trials. *Br J Cancer*. 2020;122(8):1260-1270.
86. van der Meij BS, Mazurak VC. Fish oil supplementation and maintaining muscle mass in chronic disease: state of the evidence. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2020;23(3):164-173.
87. Zhang Q, Zhu B, Li Y. Resolution of Cancer-Promoting Inflammation: A New Approach for Anticancer Therapy. *Front Immunol*. 2017;8:71.
88. Sulciner ML, Serhan CN, Gilligan MM, et al. Resolvins suppress tumor growth and enhance cancer therapy. *Journal of Experimental Medicine*. 2018;215(1):115-140.
89. Prevete N, Liotti F, Illiano A, et al. Formyl peptide receptor 1 suppresses gastric cancer angiogenesis and growth by exploiting inflammation resolution pathways. *OncoImmunology*. 2017;6(4):e1293213.
90. Schaller MS, Zahner GJ, Gasper WJ, et al. Relationship between the omega-3 index and specialized pro-resolving lipid mediators in patients with peripheral arterial disease taking fish oil supplements. *Journal of Clinical Lipidology*. 2017;11(5):1289-1295.
91. Dalli J, Serhan CN. Pro-Resolving Mediators in Regulating and Conferring Macrophage Function. *Front Immunol*. 2017;8:1400.
92. Serhan CN. Discovery of specialized pro-resolving mediators marks the dawn of resolution physiology and pharmacology. *Molecular Aspects of Medicine*. 2017;58:1-11.
93. Uno H, Furukawa K, Suzuki D, et al. Immunonutrition suppresses acute inflammatory responses through modulation of resolvin E1 in patients undergoing major hepatobiliary resection. *Surgery*. 2016;160(1):228-236.

94. Qiao Y, Yang T, Gan Y, et al. Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. *BMC Cancer*. 2018;18(1):288.

95. Gilligan MM, Gartung A, Sulciner ML, et al. Aspirin-triggered proresolving mediators stimulate resolution in cancer. *Proc Natl Acad Sci USA*. 2019;116(13):6292-6297.

96. Panigrahy D, Gartung A, Yang J, et al. Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. *Journal of Clinical Investigation*. 2019;129(7):2964-2979.

97. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality. *Br Med J*. 2016;353:1-14.

98. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *The Lancet*. 2019;393(10170):434-445.

99. Zong G, Gao A, Hu FB, Sun Q. Whole Grain Intake and Mortality From All Causes, Cardiovascular Disease, and Cancer: A Meta-Analysis of Prospective Cohort Studies. *Circulation*. 2016;133(24):2370-2380

100. Zhang X-F, Wang X-K, Tang Y-J, et al. Association of whole grains intake and the risk of digestive tract cancer: a systematic review and meta-analysis. *Nutr J*. 2020;19(1):52.

101. McNabney S, Henagan T. Short Chain Fatty Acids in the Colon and Peripheral Tissues: A Focus on Butyrate, Colon Cancer, Obesity and Insulin Resistance. *Nutrients*. 2017;9(12):1348.

102. Śliżewska K, Markowiak-Kopeć P, Śliżewska W. The Role of Probiotics in Cancer Prevention. *Cancers*. 2020;13(1):20.

103. Sehrawat N, Yadav M, Singh M, et al. Probiotics in microbiome ecological balance providing a therapeutic window against cancer. *Semin Cancer Biol.* 2020. In press.

104. Eslami M, Yousefi B, Kokhaei P, et al. Importance of probiotics in the prevention and treatment of colorectal cancer. *J Cell Physiol*. 2019;234(10):17127-17143.

105. Badgeley A, Anwar H, Modi K, Murphy P, Lakshmikuttyamma A. Effect of probiotics and gut microbiota on anti-cancer drugs: Mechanistic perspectives. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*. 2020;1875(1):188494.

106. Xu X, Lv J, Guo F, et al. Gut Microbiome Influences the Efficacy of PD-1 Antibody Immunotherapy on MSS-Type Colorectal Cancer via Metabolic Pathway. *Front Microbiol*. 2020;11:814.

107. Zambirinis CP, Pushalkar S, Saxena D, Miller G. Pancreatic Cancer, Inflammation, and Microbiome. *The Cancer Journal*. 2014;20(3):195-202.

108. Pushalkar S, Hundeyin M, Daley D, et al. The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression. *Cancer Discov*. 2018;8(4):403-416.

109. Varian BJ, Goureshetti S, Poutahidis T, et al. Beneficial bacteria inhibit cachexia. *Oncotarget*. 2016;7(11):11803-11816.

110. Chang C-W, Liu C-Y, Lee H-C, et al. Lactobacillus casei Variety rhamnosus Probiotic Preventively Attenuates 5-Fluorouracil/Oxaliplatin-Induced Intestinal Injury in a Syngeneic Colorectal Cancer Model. *Front Microbiol*. 2018;9:983.

111. Liu T, Wu Y, Wang L, et al. A more robust guy microbiota in calorie-restricted mice is associated with attenuated intestinal injury caused by the chemotherapy drug cyclophosphamide. *mBio*. 2019;10(2):e02903-18.

112. Grimble G, Ryall J. Editorial: Ketogenic diets and tumour hypoxia – kulturkampf and 'the insurgency.' *Current Opinion in Clinical Nutrition & Metabolic Care*. 2019;22(4):243-249.

113. Weber DD, Aminzadeh-Gohari S, Tulipan J, Catalano L, Feichtinger RG, Kofler B. Ketogenic diet in the treatment of cancer – Where do we stand? *Molecular Metabolism*. 2020;33:102-121.

114. Klement R, Kämmerer U. Is there a role for carbohydrate restriction in the treatment and prevention of cancer? *Nutr Metab*. 2011;8:75.

115. Abdelwahab MG, Fenton KE, Preul MC, et al. The Ketogenic Diet Is an Effective Adjuvant to Radiation Therapy for the Treatment of Malignant Glioma. Canoll P, ed. *PLoS ONE*. 2012;7(5):e36197.

116. Poff AM, Ari C, Seyfried TN, D'Agostino DP. The Ketogenic Diet and Hyperbaric Oxygen Therapy Prolong Survival in Mice with Systemic Metastatic Cancer. Tang C-H, ed. *PLoS ONE*. 2013;8(6):e65552.

117. Erickson N, Boscheri A, Linke B, Huebner J. Systematic review: isocaloric ketogenic dietary regimes for cancer patients. *Med Oncol*. 2017;34(5):72.

118. Soeters PB. Editorial: Ketogenic diets what is the benefit? *Current Opinion in Clinical Nutrition & Metabolic Care*. 2019;22(4):311-313.

119. Lee C, Raffaghello L, Brandhorst S, et al. Fasting Cycles Retard Growth of Tumors and Sensitize a Range of Cancer Cell Types to Chemotherapy. *Science Translational Medicine*. 2012;4(124):124.

120. Klement RJ. The emerging role of ketogenic diets in cancer treatment. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2019;22(2):129-134.

121. Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A Systematic Review of Exercise Systematic Reviews in the Cancer Literature (2005-2017). *PM&R*. 2017;9(9):S347-384.

122. Mctiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. *Medicine & Science in Sports & Exercise*. 2019;51(6):1252-1261.

123. Lira FS, Yamashita AS, Rosa JC, et al. Hypothalamic inflammation is reversed by endurance training in anorectic-cachectic rats. *Nutr Metab (Lond)*. 2011;8(1):60.

124. Pedersen L, Idorn M, Olofsson GH, et al. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metabolism*. 2016;23(3):554-562.

125. Eschke R-CK-R, Lampit A, Schenk A, et al. Impact of Physical Exercise on Growth and Progression of Cancer in Rodents—A Systematic Review and Meta-Analysis. *Front Oncol*. 2019;9:35.

126. Devin JL, Hill MM, Mourtzakis M, Quadrilatero J, Jenkins DG, Skinner TL. Acute high intensity interval exercise reduces colon cancer cell growth. *J Physiol*. 2019;597(8):2177-2184.

127. Gilchrist SC, Howard VJ, Akinyemiju T, et al. Association of Sedentary Behavior With Cancer Mortality in Middle-aged and Older US Adults. *JAMA Oncol*. 2020;6(8):E1-E8.

128. Ferioli M, Zauli G, Maiorano P, Milani D, Mirandola P, Neri LM. Role of physical exercise in the regulation of epigenetic mechanisms in inflammation, cancer, neurodegenerative diseases, and aging process. *J Cell Physiol*. 2019;234(9):14852-14864.

129. Vermillion SA, James A, Dorrell RD, et al. Preoperative exercise therapy for gastrointestinal cancer patients: a systematic review. *Syst Rev*. 2018;7(1):103.

130. Singh F, Newton RU, Galvão DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surgical Oncology*. 2013;22(2):92-104.

131. de van der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. *Annals of Oncology*. 2018;29(5):1141-1153.

132. Jeejeebhoy K, Dhaliwal R, Heyland DK, et al. Family physician-led, team-based, lifestyle intervention in patients with metabolic syndrome: results of a multicentre feasibility project. *CMAJ Open*. 2017;5(1):E229-E236.

133. Leung AWY, Chan RSM, Sea MMM, Woo J. An Overview of Factors Associated with Adherence to Lifestyle Modification Programs for Weight Management in Adults. *IJERPH*. 2017;14(8):922