Int.J.Curr.Microbiol.App.Sci (2023) *12*(04): 149-160

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 12 Number 4 (2023)**
Journal homepage: http://www.ijcmas.com

Review Article

https://doi.org/10.20546/ijcmas.2023.1204.017

A Review on Nutritional Interventions in Oncological Diseases of Small Animals

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Keywords

Cancer, Cachexia, Malnutrition, Weight loss, Nutritional supplements

Article Info

Received:
05 March 2023
Accepted:
01 April 2023
Available Online:
10 April 2023

A B S T R A C T

Cancer is a complex disease that results from multiple interactions between genes and the environment, and considered as leading causes of mortality in dogs and cats. Decreased food intake and metabolic abnormalities are seen in cancer patients, which in turn are associated with delayed recovery, as well as increased mortality. Metabolic condition called cachexia, is normally seen in cancer patients and is characterized by systemic inflammation, negative protein and energy balance, and weight loss. Nutrition therapy helps cancer patients to maintain healthy body weight, keep body tissue healthy, and decrease side effects both during and after treatment. Nutritional intervention in cancer patients aim to identify, prevent and treat malnutrition through the use of nutritional supplements. Foods that are low in simple carbohydrates with moderate amounts of high-quality protein, fiber, and fat (especially fats of the omega-3 fatty acid series) have been reported beneficial for cancer patients. The objective of the present review was to bring to light the most recent literature, summarise it and discuss the findings focusing on the benefits of appropriate nutritional inventions during oncological disease conditions in dogs and cats.

Introduction

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body (Preethi *et al.*, 2021). Cancer develops through multiple molecular mechanisms due to alterations at the genetic and epigenetic levels (Takeshima and Ushijima, 2019). Cancer is among the most common causes of death for dogs and cats, it is uncommon in wildlife and other domestic animals (Sarver *et al.*, 2022). Mammary cancer, skin cancer, bone cancer, mouth (oral) cancer, connective tissue cancers (sarcomas), and lymphatic tissue cancers (lymphomas) are most frequently found Dogs and Cats (Pinello *et al.*, 2022b). Tumour cells depend upon host for their nutrients supply and any modifications to the host's diet can alter nutrient availability in the tumour microenvironment, which

can be utilized as a promising strategy for inhibiting tumour growth (Kanarek *et al.,* 2020). Metabolic alterations like cachexia, commonly seen in cancer patient is a multifactorial syndrome characterized by an involuntary, sustained loss of weight and skeletal muscle mass and leads to severe functional decline (de Las Peñas *et al.,* 2019). Cancer treatment involves radiation therapy, chemotherapy, hormone therapy, surgery which can also cause loss of appetite, loss of energy, and malnutrition (Gangadharan *et al.,* 2017; Muscaritoli *et al.,* 2021). An altered host metabolic response with abnormalities in protein, lipid, and carbohydrate metabolism is seen in cancer patients (Virizuela *et al.,* 2018). Nutrition is an essential part of cancer treatment, recovery, and prevention of cancer (Ravasco, 2019). There is evidence that foods relatively low in simple carbohydrates with moderate amounts of high-quality protein, fiber, and fat (especially fats of the omega-3 fatty acid series) are beneficial for cancer patients (Tripathi *et al.,* 2005). Despite the potentially important roles of diet and nutrition in cancer prevention, the evidence to support these roles is widely perceived by the public and health professionals as being inconsistent. There is lack of studies on nutritional interventions in veterinary cancer patients. A multidisciplinary approach with targeted nutrition is vital to improve the quality of care in oncology.

Cancer/Neoplasia/Tumour & its causes & types

Cancer/Neoplasia/Tumour can be classified into two broad types: Benign tumors (produce local pressure or cause obstruction) & Malignant tumor (able to invade locally and metastasize distantly) (Pinello *et al.,* 2022a). Canine cancer occurs spontaneously and shares a similar pathophysiology and clinical manifestation with that of human analogs (Ambrosio *et al.,* 2022).

There are numerous factors that contribute to cancer like genetics, age, environment and certain viruses (Ugai, *et al.,* 2022). Some types of tumors occur more frequently in certain breeds of dogs, such as Golden Retrievers, Boxers, and Rottweilers (Dobson, 2013). In contrast to humans, pets have a shorter life span and cancer progression is often more rapid (Giuliano, 2022). Pets develop cancer more frequently during the late stages of their lives (Creevy *et al.,* 2019). It is believed to be linked to a weakening immune system as pet age.

Environmental hazards or chemicals can increase the risk of cancer (Giuliano, 2022). Some examples include a variety of herbicides, pesticides, and other chemicals. Viruses are known causes of some cancers in pets. For example, feline leukemia virus (Rolph and Cavanaugh, 2022).

The following are the most common types of tumors in pets:-

Skin tumor

Mast Cell Tumors (MCT) & Squamous cell carcinoma (SCC), are the most common skin tumors in dogs (Castro *et al.,* 2019). Squamous cell carcinoma (SCC), which arises from the cells lining the oral cavity, is the most common oral tumor in cats (Treggiari *et al.,* 2021).

Lymphoma

Lymphoma is a cancer of the lymphatic system of the body. Diffuse large B-cell lymphoma (DLBCL) is the commonest lymphoma in both humans and dogs (Riva *et al.,* 2022). The feline leukemia virus (FeLV) has been shown to cause lymphoma in some cats (Hartmann *et al.,* 2021). A classic sign of lymphoma is large, firm lymph nodes, usually found around the jaw, in front of the shoulder, or in the back of the knees.

Osteosarcoma

Osteosarcoma is the most common primary bone neoplasm in dogs and often involves the appendicular skeleton (Al-Khan *et al.,* 2020). The pulmonary parenchyma and other skeletal sites are the most common metastatic locations (Parachini-Winter *et al.,* 2019).

Mammary Gland Carcinoma

Mammary gland carcinomas are tumors that arise from the mammary or breast tissue of dogs. They account for 25–50% of all tumors diagnosed in bitches (Collivignarelli *et al.,* 2021).

Lipoma

Lipomas are benign growths arising from fat cells. Lipomas are masses of mesenchymal origin, comprising of adipocytes, and are often clinically unremarkable (O'Neill *et al.,* 2018).

Nutritional issues in malignant Diseases

Many factors that affect the nutritional status of cancer patients, including:

Ongoing tumor–host competition for dietary energy substrates (Bauer *et al.,* 2011).

Hormonal and inflammatory factors (Peixoto da Silva *et al.,* 2020); (Khatib *et al.,* 2018).

Use of anti-cancerous therapies (Joly *et al.,* 2019).

Cancer and cancer treatments may affect taste, smell, appetite, and the ability to eat enough food or absorb the nutrients from food (Rakhmanovna, 2022). Decreased food intake and metabolic abnormalities can lead to nutrition-related disorders in cancer patients, which in turn are associated with delayed recovery, as well as increased morbidity and mortality (Reber *et al.,* 2021). The digestion and absorption of nutrients like protein, carbohydrates, and fat may change when tumors are in the stomach, intestines, or head and neck (Nicolini *et al.,* 2013). The anorexia associated with cancer cachexia is likely caused by the activity of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and growth differentiation factor 15, that are produced either by the tumor or by the host in response to the tumor, which interfere with appetite signals within the anterior hypothalamus (Peixoto da Silvaet *et al.,* 2020). Side effects from chemotherapy & radiation therapy may cause problems with eating and digestion (O'Reilly *et al.,* 2020). Chemotherapy and radiotherapy damage cells in the gastrointestinal tract, food intake decrease because of nausea and vomiting, absence of appetite, diarrhea and constipation (Geraghty, 2021). Chemotherapy drugs work by stopping or slowing the growth of cancer cells (Satapathy *et al.,* 2023). Healthy fast growing cells in the mouth and digestive tract may also be killed because of non-selective and their cytotoxic impact affects both healthy normal cells as well as malignant cells (Stout and Wagner, 2019). Surgery that removes all or part of certain organs can affect a patient's ability to eat and digest food (Santarpia *et al.,* 2011). The side effects of immunotherapy are different for each patient and the type of immunotherapy drug given.

Effect on body metabolism

Anorexia is a common symptom in patients with cancer (loss of appetite or desire to eat) (Hariyanto and Kurniawan, 2021). Anorexia may occur early in the disease or later, if the cancer grows or spreads. Anorexia is the most common cause of malnutrition in cancer patients (Kang *et al.,* 2019). Some pets develop a condition called cancer cachexia, which is a complex metabolic syndrome characterized by involuntary skeletal muscle loss and is associated with poor clinical outcome, decreased survival and negatively influences cancer therapy (Van de Worp *et al.,* 2020). It is caused by factors of catabolism produced by tumors in the systemic circulation as well as physiological factors such as the imbalanced inflammatory activation, proteolysis, autophagy, and lipolysis (Ni and Zhang, 2020). Studies suggest that muscle wasting during cancer results from an imbalance between degradation and protein synthesis, mediated specially by cytokines and reactive oxygen species (Powers *et al.,* 2016). Cachexia causes loss of appetite anorexia decreased muscle mass & uncontrolled weight loss (Yeom and Yu, 2022). Cancer cachexia is caused by cancer induces abnormalities in lipid, carbohydrate, and protein metabolism which reduces the efficiency of

energy metabolism (Cao *et al.,* 2010). Cancer cachexia not only negatively affects the quality of life of patients with cancer but also reduces the effectiveness of anti-cancer chemotherapy and increases its toxicity, leading to increased cancer-related mortality (Ni and Zhang, 2020). Chronic insulin resistance is develop in cancer cachexia due to chronic exposure of proinflammatory cytokines and insulin growth factor binding protein, which results in insulin resistance (Wagner and Petruzzelli, 2015; Wang and Ye, 2015). Thus, most of the glucose induced is used by the cancer cells; hence, cancer patients have a very high energy demand (Kim, 2019). Adequate nutritional support is the main method of cachexia treatment. Albumin and CRP levels are currently considered to be the best indicators of cancer cachexia (Takayoshi *et al.,* 2017). The upregulation of pro-inflamma- tory cytokines and ROS formation may promote muscular catabolism via the ubiquitin–proteasome (Ub) system, which is considered the main mechanism responsible for the enhanced muscle protein degradation in cancer cachexia (Yuan *et al.,* 2015).

Effect on nutrient metabolism

The ability of amino acids to stimulate protein synthesis in cancer patients is reduced. In cancer cachexia, muscle protein breakdown produces amino acids needed for the inflammatory protein synthesis (Peixoto da Silva *et al.,* 2020). It is well known that impairment of carbohydrate & Lipid metabolism metabolism occurs in cancer patients (Kim, 2019). In cancer, the main pathway for glucose consumption is the transformation to lactate, to produce adenosine triphosphate (ATP) which is a much faster process than tricarboxylic acid cycle (TCA cycle) occurring in mitochondria (Farhadi *et al.,* 2020). However, this path- way has low output which results in more glucose consumption and several other metabolites. The loss of adipose tissue by metabolic impairment further promotes cancer-associated cachexia. Free fatty acid and glycerol from triglyceride increase in patients with cancer-associated cachexia (Joshi and Patel, 2022). This lipolysis is promoted by hormones, pro-inflammatory cytokines, and lipid-mobilizing factor (Malla *et al.,* 2022).

Nutritional intervention

For cancer patients, the goal is to maintain weight, although underweight pets should gain weight and some overweight pets may benefit from losing some weight. Pets with cancer can be fed home-cooked diets, commercial diets, or a combination. The challenge with home-cooked diets is that unless they are carefully designed, nutrient deficiencies are common (Larsen *et al.,* 2012). Unfortunately, there is very limited scientific knowledge about the ideal nutritional modification during cancer treatment for pets. The combination of high quality nutrients in a multitargeted, multinutrient approach appears specifically promising, preferentially as a multimodal intervention, although more studies investigating the optimal quantity and combination of nutrients are needed (Van de Worp *et al.,* 2020).

Ketogenic diet

Recently, ketogenic diet has been newly emerged as a cancer therapy in both animal models and humans. Ketogenic diet are defined as diets high in fat, low in carbohydrate and a protein content to meet requirements (Allenspach *et al.,* 2022). The modulation of cellular metabolism by carbohydrate depletion via ketogenic diets has been suggested as an important therapeutic strategy to selectively kill cancer cells (Chung and Park, 2017).

Low carbohydrate content in ketogenic diet leads to increased fat metabolism and elevated levels of fat-derived ketone in the blood. Since glucose is the main source of energy for cancer cells (the Warburg effect), a reduction in the availability of this fuel can be beneficial, controlling the proliferation and metastatic capacity (Branco *et al.,* 2016). Low calorie diet, such as fasting inducing a state of ketosis, has been shown to enhance the responsiveness of cancer cells to chemotherapy in pre-clinical cancer therapy models and to ameliorate

some of chemotherapy-induced side effects in normal tissues (Lee *et al.,* 2012).

Protein & Amino acids supplementation

Cancer patients display systemic inflammation, which leads to an increase in protein catabolism, thus promoting the release of free amino acids to further support metabolism (Soares *et al.,* 2020). Recent researches suggested an adequate supply of dietary protein is a prerequisite for maintenance or gain of skeletal muscle mass (Prado *et al.,* 2020). Nutrients, such as amino acids (AAs), are not only a caloric source, but can also modulate cell metabolism and modify hormone homeostasis (Bonfili *et al.,* 2017). Muscle mass supplements, such as L-leucine (including whey protein and branched-chain amino acids), β-hydroxy-beta-methyl butyrate (HMβ), arginine, and glutamine, several studies have carefully examined their effects. L-leucine and its derivatives appear to regulate protein synthesis and promote muscle protein balance (Soares *et al.,* 2020). Arginine and glutamine may act by reducing inflammation and infection progression, thus promoting improvements in food intake (Prado *et al.,* 2020; Holbert *et al.,* 2022). Glutamine is a nonessential amino acid that serves an important role in the metabolism and immune system, is considered a nutritional supplement for cancer patients (Kim, 2019). Glutamine levels are reduced in cancer patients because glutamine is used as the energy source by cancer cells (Jiang *et al.,* 2019). Glutamine supplementation is usually focused on preventing side effects that may occur during chemotherapy or radiotherapy, especially in gastrointestinal mucosal protection.

Fat & Fatty acids

Dietary fat is an important source of energy and contributes a significant caloric value to our diet. Consequently, a high fat diet might be expected to prevent host catabolism during cachexia, mainly by tumor growth reduction. Omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, serve as natural anti-inflammatories in cells by inhibiting cyclooxygenase (Islam *et al.,* 2022). Several mechanisms have been proposed to explain the potential benefits of EPA & DHA on the body composition: inhibition of catabolic stimuli by modulating the production of pro-inflammatory cytokines and enhancing insulin sensitivity that induces protein synthesis (Al-Jawadi *et al.,* 2020). Diet supplementation with fish oil (rich in Omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid) has been investigated to preserve skeletal muscle mass in various experimental animal models of cancer cachexia (Liu *et al.,* 2019). Flaxseed (one of the richest plant sources of the ω-3 fatty acid i.e. α-linolenic acid) has shown to have health imparting benefits in decreased risk of cancer, particularly of the mammary and prostate gland (Goyal *et al.,* 2014). Omega-3 fatty acids also may be able to kill cancer directly and have been shown to reduce cellular proliferation, angiogenesis and invasion, and increase programmed cell death (West *et al.,* 2020; Haidari *et al.,* 2019). Conjugated linoleic acid (CLA) found mostly in red meat and dairy products has shown anti-carcinogenic effects (Basak and Duttaroy, 2020).

Probiotics

Probiotics play an important role in prevention and treatment of various types of cancer effectively (Bedada *et al.,* 2020). Probiotics are defined as living microorganisms that, when taken in adequate amount, offer positive health benefits to the host (Sharma, 2019). Probiotics are more effective when used with prebiotics than probiotics alone in prevention and treatment of different cancer (Bedada *et al.,* 2020). Probiotics and their probioactive cellular materials form several beneficial effects in the gastrointestinal tract, and release different enzymes and form potential synergistic effects on digestion. Probiotics are mostly categorized into bacterial or lactic acid and non-lactic acid bacteria strains, and yeasts. *Lactobacillus*, *Lactococcus*, *Bifidobacterium* and *Enterococcus* are common bacterial probiotics

(Georgiev *et al.*, 2015). The other unique features of probiotics are delaying the formation of tumor, inhibit the proliferation of cancer cells and prevent the life threatening side effects that are associated with current cancer treatment (Hassan, 2019). The results of many in vitro studies indicate beneficial properties of probiotics in modulating the proliferation and apoptosis of cancer cells including, e.g., gastric, colonic, and myeloid leukemia cells (Altonsy *et al.*, 2009). Certain probiotic microorganisms are useful in the control of various intestinal disorders, including fever, postoperative inflammatory diseases, viral diarrhea and antibiotic or chemotherapy/radiotherapy-associated diarrhea (Slizewska *et al.*, 2022). Prebiotic fibers occur naturally in certain foods, including selected legumes, grains, fruits and vegetables, and fiber-rich foods, such as whole grains, have been reported to have a prebiotic-like effect on the gut microbiota (Turati *et al.*, 2023). They have shown colorectal cancer prevention with respect to their effects on gut microbiome structure and microbial metabolite production in the colon environment (Mahdavi *et al.*, 2021).

Other supplements

Carnitine

l-Carnitine, a nutrient found primarily in red meat (Koeth *et al.*, 2019), is an amino acid-derived substance that plays important role including transport of long-chain fatty acids from the cytoplasm to the mitochondrial matrix, regulation of acetyl-CoA/CoA and protection against oxidative stress (Li and Zhao, 2021). Altered serum and urine carnitine levels have been reported in cancer patients with various forms of malignant diseases (Sayed-Ahmed, 2010). Carnitine not obtained from food is synthesized endogenously from two essential amino acids, lysine and methionine in liver and kidney (Cave *et al.*, 2008). Supplementation of carnitine to enhance mitochondrial β-oxidation may attenuate oxidative stress and inflammation, resulting in beneficial clinical outcomes (Virmani *et al.*, 2022). Carnitine supplementation has been studied in various experimental models of cancer cachexia. Carnitine supplementation improves the tolerability of chemotherapy in cancer patients by reducing general fatigue and improving the nutritional status (Matsui *et al.*, 2018).

Creatine

Creatine is a non-protein amino acid that can be endogenously synthesized in the liver, kidney and pancreas and is mainly stored and utilized in the skeletal muscle (Van de Worp *et al.*, 2020). Creatine is naturally found in animal tissues such as meats, fish, and poultry (Kaviani *et al.*, 2020). Creatine supplementation has shown antioxidant capacities as well as effectiveness to counteract pro-inflammatory cytokines in cancer cachexia (Cella *et al.*, 2020; Costa Godinho *et al.*, 2023). Creatine exerts anabolic activity, acting as an immediate energy substrate to support muscle contraction further increasing lean mass, mainly due to greater water uptake by the muscle (Soares *et al.*, 2020). Despite the promising results, only a few studies have investigated the effects of creatine supplementation in experimental cancer cachexia.

Flavonoids

Flavonoids are phytochemical compounds present in many plants, fruits, vegetables, and leaves, with potential applications in medicinal chemistry (Ullah *et al.*, 2020). Flavonoids possess a number of medicinal benefits, including anticancer, antioxidant and anti-inflammatory properties (Al-Ishaq *et al.*, 2019; Chen *et al.*, 2019, Ullah *et al.*, 2020). Vegetables and fruits, whole grain cereals, legumes, seeds, and nuts are the main dietary sources of flavonoids (Rodríguez-García *et al.*, 2019).

Vitamins and minerals

There is an inherent risk of micronutrient deficiency due to malnutrition and side effects of therapy such as vomiting or diarrhea in cancer patient (Prado *et al.*, 2020). Use of a multivitamin-multimineral supplement in doses close to the recommended

dietary allowance is beneficial in cancer patient (Ravasco, 2019; Akutsu *et al.*, 2020). A low vitamin D status and inadequate calcium intake are important risk factors for various types of cancer (Peterlik *et al.*, 2009). The relationship of vitamin D and diseases has also been investigated in dogs and cats, and some studies found association between low vitamin D status and some types of cancer (Selting *et al.*, 2016; Weidner *et al.*, 2017). Increased intakes of α-tocopherol (AT) and/or β-carotene (BC) prevent lung cancer and other cancers in human beings (Colombo, 2010) and selectively induce cancer cells to undergo apoptosis (Kline *et al.*, 2004; Smolarek and Suh, 2011) because of its high antioxidant potential. Many studies have reported that selenium supplement decreased risk of colorectal cancer, lung cancer and bladder cancer in humans (Clark *et al.*, 1996; Michaud *et al.*, 2005; Cai *et al.*, 2016).

General management of nutritional issues

It is important to avoid feeding raw diets or treats to pets with cancer. Raw meat, eggs, and milk carry high risk of bacterial contamination with Salmonella, E. coli, Campylobacter, and other potentially dangerous bacteria (Lefebvre *et al.*, 2008; Freeman *et al.*, 2013; Nüesch-Inderbinen *et al.*, 2019).

Adjustment to the nutrient profile is required for patients with comorbidities (e.g., liver or kidney disease, pancreatitis, hyperlipidemia). Food intolerances or allergies may limit ingredient or nutrient options. A diet formulated for weight management by veterinarian should be used otherwise may lead to nutrient deficiencies.

Feeding foods that smell good, fresh food diets may be more palatable and appealing for dogs or cats with variable appetites. Choose lean meats (such as chicken or turkey) without skin.

To increase daily caloric intake, increase the feeding frequency and leave the dry food accessible throughout the day.

Cancer treatments and side effects may put patients at risk for dehydration (Stout and Wagner, 2019), fresh drinking water should be available all time.

Feed foods that are high in fiber, such as whole-grain breads, cereals and fruits.

Give exercise daily

In conclusion, nutrition plays a crucial role in cancer care. It affects treatment tolerability, outcomes, and quality of life. However, a focus on nutrition is still lacking among oncologists because of insufficient training in nutrition topics received during UG and PG training and an underestimation of its importance. The consequences of the disease and its treatment, such as anorexia, cachexia, are therefore still often overlooked, under diagnosed, and undertreated. A proactive assessment of the clinical alterations that occur during treatments and during the disease course, is essential for selecting the adequate nutritional intervention, aiming for the best impact on patients' outcomes. Further research is needed to determine the safety and efficacy of nutritional supplements. Greater emphasis is needed in veterinary practices on the importance of client and clinician communication to ensure dogs with cancer are provided a safe and healthy diet.

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How to cite this article:

Manjeet Kumar, Suman Lata and Tripta Devi. 2023. A Review on Nutritional Interventions in Oncological Diseases of Small Animals. *Int.J.Curr.Microbiol.App.Sci.* 12(04): 149-160.
doi: https://doi.org/10.20546/ijcmas.2023.1204.017