O – Oncology

NUTRITION AND CANCER: FRONTIERS FOR CURE!

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Using specifically formulated diets or dietary supplements to prevent and to treat cancer is in its infancy; however, enough information exists to begin making some recommendations to prevent and treat cancer in people and dogs.[1–5] In human medicine, several nutritional factors have been found to increase the risk and rate of developing cancer, including[3–5]:

•Obesity
•Consumption of nutrient-sparse foods, such as concentrated sugars and refined flour products
•Low fiber intake
•Inadequate consumption of polyunsaturated fatty acids of the n-3 series (n-3 PUFAs) and an increase consumption of PUFAs of the n-6 series (n-6 PUFAs)

Carbohydrates and Cancer

Evidence is mounting that simple carbohydrates may be contraindicated for the nutritional management of cancer in dogs:[1,2,6–20]

•Dogs with a wide variety of malignant conditions have elevated resting insulin and lactate levels compared to control animals.[8–11,15] It is unknown if the elevated insulin levels are a response to cancer or if they precede and possibly contribute to the development of cancer via stimulation of insulin-like growth-factor (IGF) pathways.
•Elevated lactate and glucose levels do not improve after dogs with cancer are rendered free of disease with chemotherapy and surgery[8] **(Figure 31-3).** This suggests that the malignancy causes a fundamental change in metabolism that persists after all clinical evidence of cancer is eliminated.
•Elevated lactate levels can result in inefficient Cori cycle activity to convert lactate back to glucose; this results in a net energy loss by the patient.[8–11,15]
•The administration of lactate-containing parenteral fluids such as lactated Ringer's solution has been shown to increase lactate levels in dogs with lymphoma, suggesting that these types of fluids may place an additional energy burden on the host.[9]
•Before the development of severe malnutrition, human patients with colon, gastric, sarcoma, endometrial, prostate, localized head, neck, or lung cancer have many of the metabolic abnormalities of type II (non–insulin-dependent) diabetes mellitus.[21,22] These metabolic abnormalities include glucose intolerance; an increase in hepatic glucose production, glucose recycling, and insulin resistance; and an increase in anaerobic glycolysis causing increased lactate production. These are essentially the same findings as in dogs with cancer.[1,2,6–20]

The metabolic abnormalities noted above are only important if they affect the patient clinically. Studies done in human patients suggest that alterations in carbohydrate metabolism influence cancer prevention and outcome once cancer is diagnosed.[23–25] For example, one study evaluated the hypothesis that glucose, insulin, and IGFs contribute to breast cancer development in 10,786 women.[23] It was concluded in this research that higher levels of glucose, insulin, and IGF-1 were associated with a higher risk of developing breast cancerand a poorer survival after diagnosis.A second study involving 603 breast cancer patients was performed to test the hypothesis that excess insulin and related factors are directly related to mortality after a diagnosis of breast cancer.24 It was concluded in that study that high levels of insulin were associated with poorer survival for postmenopausal women.

Proteins and Cancer

Dogs with cancer have alterations in protein

metabolism that are very similar to those observed in humans and laboratory animals with cancer.[1] For example, there is a significant decrease in a wide variety of amino acids, suggesting that a high-quality, highly bioavailable protein source would be beneficial to the animal and to the tumor. Amino acids of particular importance to patients with cancer are glutamine, cysteine, and arginine.

Glutamine supplementation may enhance the therapeutic index of chemotherapy and radiation by enhancing the efficacy of these treatments while reducing adverse effects such as mucositis, diarrhea, neuropathy, and cardiotoxicity.[27,28] Glutamine is conditionally essential for the health and function of the bowel. At least some of this amino acid is destroyed in the process of making many types of dried and canned pet food.

Cysteine is critically important to replenish the glutathione antioxidant system.[29,30] This system is the principal protective mechanism of the cell and is a crucial factor in the development of the immune response. Cysteine supplementation has been shown to have anticancer activity via the glutathione pathway, the induction of p53 protein in cancer cells, and inhibition of neoangiogenesis.[29,30]

Arginine is a conditionally essential amino acid that is necessary during periods of growth and recovery after injury. Arginine promotes wound healing, has several immunomodulatory effects such as stimulating T- and natural-killer cell activity, and influences proinflammatory cytokine levels.[31] L-Arginine is the sole precursor for the multifunctional messenger molecule nitric oxide, which appears to influence tumor initiation, promotion, and progression; tumor-cell adhesion; apoptosis angiogenesis; differentiation; chemosensitivity; radiosensitivity; and tumor-induced immunosuppression.[31] The administration of arginine to human and veterinary cancer patients has resulted in positive outcomes.

Lipids and Cancer

Serum lipid profiles were performed in dogs with lymphoma before and after they were put into remission with chemotherapy. These profiles were compared to those of normal dogs before and after they were given the same anticancer drug.[11]

- The dogs with cancer had significantly lower levels of high-density lipoproteins. The total triglyceride levels and very low-density triglycerides of untreated dogs with lymphoma were significantly higher than those of untreated control dogs.[11]
- After a total of five doses of doxorubicin chemotherapy, the total cholesterol level increased in dogs with lymphoma but decreased in treated control dogs.[11]
- All other parameters remained unchanged after doxorubicin therapy, suggesting that lipid abnormalities do not improve significantly, even after a clinical remission is obtained.[11]

We tested the hypothesis that diets relatively high in fat may be beneficial for animals with cancer compared to diets that are high in simple carbohydrates, assuming that the protein content, caloric density, and palatability remain constant. One study suggested that a high-carbohydrate, low-fat diet induced elevated lactate and insulin levels compared to a diet relatively high in fat and low in carbohydrates.[2,12] It also suggested that a high-fat diet may result in a higher probability of going into remission with chemotherapy as well as a longer survival time. The kind of fat in the diet, rather than the amount, may be the important factor. For example, n-3 PUFAs have been shown experimentally to have many beneficial properties.[2,12,16]

Emerging Role of PUFAs

For the last decade, investigators have searched for dietary lipids associated with a delay in cancer relapse. The use of long-chain polyunsaturated fatty acids (LC-PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as adjuvant therapies to enhance the effect of chemotherapy and radiation therapy shows promise. LC-PUFAs have been shown to enhance disease-free interval, survival, and quality of life after surgery by reducing the rate of cancer development or incidence. This concept, known as 'cancer prevention by delay' or clinical cancer chemoprevention, is an important mechanism behind the successes of several therapeutic agents, including tamoxifen, retinoids and interferon-alfa, and nonsteroidal anti-inflammatory drugs.[32]

Cancer prevention by delay is a valuable clinical tool until more effective cancer therapeutics can be developed. Unfortunately, while use of the most effective cancer therapies (i.e., surgery, radiation, and chemotherapy) is effective for improving the disease-free interval of many patients up to a point, it has not increased the cancer cure rate or survival time dramatically in the last 10 years. Therefore, it seems logical to add on relatively nontoxic therapies that can extend the disease-free interval, even if the absolute cure rate is not increased. Tamoxifen, retinoids, and nonsteroidal anti-inflammatory agents are all recognized to improve disease-free interval without necessarily improving the absolute cure rate. Tamoxifen has been shown to significantly diminish the risk of human breast cancer; retinoids and interferon-

alfa to reduce the risk of head and neck cancer in dogs, cats, and humans; and nonsteroidal anti-inflammatory drugs to delay or reduce the development of colorectal cancer in humans and transitional cell and squamous cell carcinomas in dogs.

Dietary lipids such as DHA and EPA appear to influence the growth of many types of cancer, including breast and prostate cancer.[33–36] A group of investigators in France used adipose tissue sampled during surgery as a biomarker of past dietary intake of PUFAs in a cohort of women treated for localized presentations of breast cancer.[37] They found elevated n-3 PUFAs, especially DHA, to be associated with a higher metastasis-free survival, suggesting that these PUFAs could potentially delay metastasis by decreasing tumor growth or development. Using a case-control approach comparing the fatty acid composition of adipose breast tissue obtained at the time of surgical removal of either malignant or benign breast tumors, they also found α-linoleic acid and docosahexaenoic acid to be positively associated with a decreased risk of having breast cancer.[38]

The French group also explored the role of n-3 PUFAs in mammary tumor growth using the experimental system of N-methylnitrosourea (NMU)-induced mammary tumors in rats. Because PUFAs are substrates for lipid peroxidation processes, the investigators studied the effects of n-3 PUFAs on tumor growth in interaction with anti- or pro-oxidant compounds. They found that dietary n-3 PUFAs, in the form of DHA-containing fish oil, inhibited tumor development. This inhibition was most evident in the absence of the antioxidant vitamin E. Inhibition of tumor growth was even greater when n-3 PUFAs were given in the presence of pro-oxidants.[340] Such effects were not found when the lipid diet was low in PUFAs. These data suggest that oxidized n-3 PUFAs have an inhibiting effect on tumor growth and emphasize the importance of the interaction of anti- and pro-oxidant compounds with n-3 PUFAs.

There is a growing body of data that suggests that the presence of n-3 PUFAs such as DHA and EPA affects several steps of tumor formation. N-3 PUFAs:

- Inhibit tumor vessel formation (angiogenesis)
- Inhibit cell proliferation in several epithelial cell lines
- Enhance the rate of tumor cell death
- Induce lipid peroxidation, which enhances the efficacy of radiation- and chemotherapy-induced cancer cell death; this effect is diminished or reduced dramatically with vitamin E
- Suppress the expression of cyclooxygenase-2 in tumors, thereby decreasing cancer cell proliferation
- Suppress nuclear factor κB activation and BCL-2 expression, thus allowing apoptosis of cancer cells

Dietary lipids have been shown to modify the sensitivity of tumors to reactive oxygen species–generating anticancer drugs. For example, when dogs with lymphoma were treated with doxorubicin chemotherapy and a diet supplemented with n-3 PUFAs in the form of fish oils, there was a direct correlation between the level of DHA in the blood and improved disease-free interval.[18] Another study, using the same randomized study design, was used to assess the efficacy of n-3 PUFAs in combination with doxorubicin chemotherapy to improve the disease-free interval in dogs with hemangiosarcoma, a highly metastatic, rapidly fatal malignancy. There was a statistically significant positive correlation between the n-3 PUFAs **levels in the serum** and disease-free interval.[39] A similar approach was used in rats bearing autochthonous, NMU-induced mammary tumors. It was found that dietary supplementation with fish oil or DHA increased the sensitivity of mammary tumors to anthracyclines, compared with dietary supplementation with saturated fatty acids.[39]

Because DHA is the most polyunsaturated of the PUFAs, lipoperoxidation is a likely molecular mechanism implicated in the enhancement of the response of cancer cells to cytotoxic drugs. Addition of vitamin E to the diet provided to rats with mammary tumors abolished the enhancing effect of DHA on tumor sensitivity to anthracyclines.[39] In all studies done to date, there has been no clinically significant toxicity other than transient gastrointestinal (GI) distress linked to the dietary change.[17,18] Therefore, based on the safety and efficacy profile of n-3 PUFAs , it seems reasonable to further define the efficacy of n-3 PUFAs, especially DHA, for the treatment of spontaneously occurring cancer in dogs, with the intent to provide evidence for their use in randomized human clinical trials.

DHA and EPA also augment the efficacy of chemotherapy and radiation therapy, potentially enhancing the efficacy of traditional cancer therapies. Radiation therapy is currently the most effective treatment for many localized malignancies. Research is under way to identify methods to maximize its efficacy while minimizing the adverse effects associated with it. Among the agents being evaluated to minimize the damage to normal tissue are n-3 LC-PUFAs, which are readily incorporated into cell membranes and ameliorate inflammation and carbohydrate dyshomeostasis. In one study, 12 dogs with histologically confirmed malignant carcinomas of the nasal cavity were randomized to receive

isocaloric amounts of a diet supplemented with menhaden fish oil, including DHA (experimental diet), or an otherwise identical diet supplemented with corn oil (control diet). Megavoltage radiation was delivered to all dogs. The data in this study suggest that feeding a diet supplemented with fish oil and arginine is associated with decreased concentrations of inflammatory mediators involved with radiation damage in skin and mucosa and with improved performance scores in dogs with malignant nasal tumors.[41]

The ability of PUFAs to sensitize tumors to radiation has been investigated. Vartak et al[42,43] studied the in vitro response of a chemically induced rat malignant astrocytoma cell line to radiation after the cell culture medium was supplemented with g-linoleic acid (GLA) or n-3 LC-PUFAs. They found that n-3 PUFAs enhanced radiation-induced cell cytotoxicity. In a separate study, Colas et al[44] documented enhanced radiosensitivity of rat autochthonous mammary tumors after administration of dietary DHA.

Whether use of dietary n-3 PUFAs can enhance sensitivity of tumor tissue in the absence of a similar increase in the radiosensitivity of nontumor tissue remains a critical issue. Several studies have suggested that PUFAs do not sensitize normal tissue to radiation. For example, because ionizing radiation generates reactive oxygen species, we initiated a study to determine whether dietary DHA might sensitize mammary tumors to irradiation using a model in which mammary tumors were induced by NMU in Sprague-Dawley rats. In the study, we showed that dietary DHA sensitized mammary tumors to radiation. The addition of vitamin E inhibited the beneficial effect of DHA, suggesting that this effect might be mediated by oxidative damage to the peroxidizable lipids.[44]

References

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