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ENVIRONMENTAL CAUSES OF CANCER IN PETS

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Epidemiology and Cancer

One of the most common questions clients ask their veterinarian is, "What caused my dog or cat's cancer?" The answer to that question is difficult to answer, but as in man, the etiopathogenesis of cancer in canine oncology often involves genetics and environmental risk factors. Indeed, Bernese Mountain dogs have been shown to have a high rate of cancer when compared to other breeds. Similarly, exposure to cigarette smoke, asbestos and other environmental contaminants have been associated with an increased risk of developing cancer in dogs. Therefore, the prevention of cancer is based on the identification of at-risk animals based on familial/genetic and environmental influences. Epidemiology is the science that begins to identify these genetic and environmental influences that can then be used for cancer prevention.

The identification of factors associated with an increased risk of developing cancer is in its infancy in veterinary epidemiology and oncology. Despite this early state of development, several important observations can be made. Clients should be educated that increased risk does not equal causality in all animals; in other words, exposure to a risk factor does not automatically equate with having caused their pet's cancer. Often an environmental factor may act in conjunction with genetic and other lifestyle factors to further increase risk of cancer.

Causes of Cancer in dogs

Nutrition: A life time study of restricted daily intake of the same food was done with a total of 48 control-fed vs paired restricted-fed (25% less intake) Labrador retriever dogs numbering from 7 litters. The median life span of the restricted-fed group was significantly longer. While the prevalence of cancer between groups was similar, the mean age due to cancer related deaths was two years later in the dogs that received the restricted diet.

Increased consumption of green leafy vegetables and yellow-orange vegetables decreased the risk of urinary bladder TCC in genetically predisposed dogs (Scotties) in one study.

Some practical suggestions might be:

- Restrict daily intake to maintain a thin body weight throughout life.
- Supplement diet with vegetables at least 3 times per week.

Ovariohysterectomy/Orchiectomy: Ovariohysterectomy has long been demonstrated to be a markedly effective method of preventing mammary tumors if it is performed before the first estrus. Spaying is moderately effective if performed before the dog is 2.5 years of age. Spaying may also be therapeutic when treating dogs with mammary tumors.

Orchiectomy will reduce the risk of testicular tumors.

Gonadectomy may not uniformly protect against all cancers. A study of Rottweiler dogs showed that male and female Rottweiler dogs that underwent gonadectomy before 1 year of age had an approximate one in four lifetime risk for bone sarcoma and were significantly more likely to develop bone sarcoma than dogs that were sexually intact.

Genetics: There is little doubt that cancer occurs more often in certain breeds and that environmental factors may influence these factors. German shepherd dogs have been shown to have bilateral cystadenocarcinomas and cutaneous sarcomas. Flat-coated retrievers (and Bernese mountain dogs) have been shown to have a high incidence of cancer including malignant histiocytosis. Scottish terriers, especially those with exposure to herbicides have an increased risk of developing transitional cell carcinomas of the bladder.

Environmental Carcinogens: In sharing their living environment with humans, pets are exposed to many of the same environmental contaminants as their owners, including environmental tobacco smoke (ETS). In fact, exposure levels in animals kept indoors continuously may be higher than those of human household members, who often spend extended periods of time outside the home.

Dogs have been shown to have an increased risk of developing cancer of the respiratory tract, especially of the lung and nasal cavity when exposed to coal and kerosene heaters and passive tobacco smoke. One veterinary study found a weak association with exposure to tobacco in the home (odds ratio 1.6), but no dose-response relationship. The risk rose for dogs with short or medium length nasal cavities. In a similar study, dogs of long-nosed breeds had an increased risk of developing nasal cancer when exposed to ETS than did dogs of breeds with shorter noses.

Mesothelioma is more common in dogs owned by people who worked in the asbestos industry.

Lymphoma was more common in dogs that lived in an urban environment in one study. In addition, the use of chemicals by owners, specifically 2,4-D, paints, asbestos or solvents, as well as radiation and electromagnetic field exposure were associated with increased risk for canine lymphoma.

Application of insecticides (but not in a spot-on formulation) increased the risk of bladder cancer in Scottish terriers in another study.

Some practical suggestions might be:

- Eliminate exposure to environmental carcinogens such as pesticides, coal or kerosene heaters, herbicides such as 2, 4-D, passive tobacco smoke, asbestos, radiation and strong electromagnetic field exposure. These steps may be particularly important for owners of susceptible breeds (for example a Scottish terrier and herbicide exposure).

Environmental Causes of Cancer in Cats

Feline Hyperthyroidism

There is unlikely to be a single for etiologic reason for the increase in incidence of thyroid adenomas during the 1980's and 1990's.

Two studies have examined the risk factors for hyperthyroidism in cats. In the most recent study, Himalayan cats and in both studies, Siamese cats were found to be at decreased risk of developing hyperthyroidism. This is consistent with breed descriptions of large series of hyperthyroid cats. Interestingly, relatives of hyperthyroid cats were more likely to be hyperthyroid, as were cats that lived in the same household. Cats that ate more than 50% of their diet as canned cat food had an increased risk of becoming hyperthyroid, as did cats that used kitty litter. Being an indoor cat also appeared to increase risk. There was no effect of neutering, number of cats in the household, use of dietary supplements or

medications or frequency of vaccination. Factors that increased risk, but were not independent of those stated above, were high level of smoking by owner, and use of flea products. The use of flea products was found to increase risk in one study, but in the other study their risk was not related to frequency of usage (or "dosage"). Supplementation of diet with beef or poultry decreased the risk of disease, but again, this factor was not independent of those stated above. Viral causes appear unlikely, and one study found no association between FIV infection and hyperthyroidism.

We have been interested in the effects on pet animals of living with owners that smoke, thereby potentially exposing pets to "second-hand" or environmental tobacco smoke (ETS). Routes of ETS exposure in cats may be through inhalation and oral ingestion during grooming of particulate matter deposited on the fur. Like humans, cats exposed to ETS metabolize nicotine into cotinine and demonstrate urinary cotinine levels that increase with quantity of exposure (Bertone, unpublished data). Because cats have a shorter lifespan than humans, it is relatively easy to observe the effect of a long-term ETS exposure on lifetime risk of lymphoma or SCC. We therefore conducted a hospital-based case-control study of exposure to environmental tobacco smoke and risk of oral SCC or lymphoma in cats presenting to the Tufts University School of Veterinary Medicine (TUSVM).

Squamous cell carcinoma

SCC is the most frequently occurring oral neoplasm in both humans and the domestic cat. This tumor is highly locally invasive, frequently ulcerative, and often causes lytic changes in underlying bony structures. Common presenting symptoms include ptyalism, halitosis, and mechanical interference with food prehension. These tumors have a relatively low rate of metastasis, but may spread to regional lymph nodes, and rarely lungs. Effective therapies are few. Even with aggressive treatment including radical surgery, radiation therapy and adjunctive chemotherapy, survival rates past one year are typically less than 10%. Without treatment, affected cats are usually euthanized within 4-6 weeks of diagnosis due to complications associated with local disease.

Until recently, the etiology of this feline tumor was poorly understood. In humans there is a strong link between the development of SCC and the use of tobacco products such as cigars, cigarettes and chewing tobacco. More recent studies have solidified this link by demonstrating the presence of adducts between DNA and tobacco related carcinogens in these neoplasms and in oral squamous cells of individuals using tobacco products. Because domestic cats groom extensively, their alimentary tract, particularly the oral cavity, may be exposed to particulate matter deposited on their fur. These particles may include chemicals present in applied products such as flea powders and those present in environmental contaminants such as cigarette smoke. The most common site for oral SCC in cats is the ventral aspect of the tongue caudal to the lingual frenulum. Because of anatomy, this site is likely to accumulate irritant chemicals and carcinogens. Irritation produced by repetitive grooming and other factors may also facilitate the entry of these agents into the oral mucosa. If these suppositions are correct, cats exposed to environmental carcinogens such as ETS would be more likely to develop oral SCC than cats not exposed.

Based on studies performed by us, we found that exposure to ETS was associated with a non-significant increase in risk of oral SCC. Cats with any exposure to household ETS had 1.5 times the risk of oral SCC as those with no ETS exposure. Although cats exposed to environmental tobacco smoke for a period of time greater than 5 years, and cats living with 2 or more smokers were 1.6 times and 2.0 times as likely, respectively, to develop SCC than those with no ETS exposure, results were not statistically significant. High intake of both canned cat food and canned tuna fish were associated with an increased risk of oral

SCC compared to cats with low intake of each food type. In addition, we observed a significant 3-fold increase in risk of SCC in cats with a history of flea collar use. In contrast, cats with any history of flea shampoo use were at significantly lower risk of SCC.

Of the 23 biopsies evaluated for p53 expression, 15 (65%) demonstrate positive nuclear staining. Tumor biopsies from cats exposed to any ETS were 4.5 times more likely to overexpress p53 than were tumors from unexposed cats (P=0.19). Among cats with any ETS exposure, those with 5 years or more exposure were 7.0 times more likely to overexpress p53 (P=0.38). Longhaired cats (p=0.18) and female cats (p=0.35) were also more likely to show p53 expression in their tumors. These results provided additional support for a relationship between oral SCC development and exposure to household ETS, and may implicate p53 as a potential site for ETS-carcinogen-related mutation in feline oral SCC.

Lymphoma is a common malignancy in domestic cats and is histologically similar to human NHL. Previously, feline lymphoma was believed to be largely the result of infection by feline leukemia virus (FeLV), with the majority of cats diagnosed with lymphoma also testing positive for FeLV. However, in recent years vaccination for FeLV, and separation of cats that test positive on serology, have greatly reduced the prevalence of infection in domestic cats, and the proportion of lymphoma cases with concurrent FeLV infection has substantially decreased. The reduced role of FeLV in the etiology of feline lymphoma raises questions about whether lifestyle and environmental factors may influence disease risk as they do in humans. Several recent studies have suggested that smoking may significantly increase the risk of non-Hodgkin's lymphoma (NHL) in humans, although results have been inconsistent. Of the four cohort studies to evaluate this association, three observed a significant increase in risk of NHL in current smokers, with relative risks ranging from 1.4 to 3.8. A positive association between smoking and NHL has also been suggested by the results of several, but not all, case-control studies of this relationship. Although the relationship between parental smoking prior to a child's birth and risk of childhood lymphoma has been evaluated, few studies have directly addressed the role of passive smoking in the development of NHL.

We also studied environmental exposures in cats with lymphoma (as well as SCC and cats with renal disease). After adjustment for age, location of residence and hair length, the relative risk (RR) of lymphoma for cats with any household ETS exposure was 2.4. Risk increased with both the duration and quantity of exposure with evidence of a linear trend. For example, cats with five or more years of ETS exposure had a RR of 3.2 compared to those living in non-smoking households. These findings were statistically significant, and suggest that household smoking may increase the risk of lymphoma in pet cats, and that further study of the relationship between passive smoking and human NHL is warranted.

Clearly, the impact of ETS on the health of pet cats is considerable. Living with owners who smoke appears to increase the risk for developing two of the most common cancers affecting pet cats, and increasing exposure levels may additionally increase that risk. This information should be used to inform pet owners about the importance of home exposure to ETS as a risk to the health of their cats.

References/Suggested Reading

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