

Dogs, Genes, and Cancer: Why Cancer Happens and What We Can Do to Prevent and Treat It.

Introduction. Due to advances in veterinary health care, dogs are living to older age when most cancer types occur with greater incidence. Cancer is now the leading cause of disease-related death in dogs, and as such, it has gained exceptional importance in our society. Genetic and environmental factors also have major effects on the temporal occurrence of cancer and are the basis of research on what causes cancer (pathogenesis), as well as prevention, diagnosis and treatment. Thus, a new emphasis has developed to learn more about genetic and environmental factors that influence cellular and molecular changes in canine cancer. Dogs and people are susceptible to many of the same types of cancer and the natural history of many cancer types appear to be similar in both species. The shorter life span of dogs (both in terms of life-years and generations) and the availability of extended pedigrees with detailed family histories, provide a unique opportunity to address causative issues of cancer that will be important for both dogs and people.

Cancer is a “genetic” disease. The term cancer refers to a large number of diseases whose common feature is uncontrolled cell growth and proliferation (multiplication). This loss of cell growth control results from an accumulation of mutations (errors introduced into the DNA code) in genes that control cell division and cell survival. The most common mechanism that introduces mutations into the DNA of somatic cells (non-reproductive cells) is the inherent error that occurs during normal cell division. In mammalian cells, there is an error rate of about 1 in 1,000,000 to 1 in 10,000,000 bases during each round of replication. The genome consists of many millions of base pairs, so each daughter cell is likely to carry at least a few mutations in its DNA. Most of

these mutations are silent; that is, they do not present any problems to the cell's ability to function. However, others can disable tumor suppressor genes or activate oncogenes that respectively inhibit or promote cell division and survival. A cell that accumulates sufficient mutations which eliminate steps necessary to restrain proliferation and maintain genetic integrity can give rise to a tumor. Because of the mutations, this cell and its progeny acquire a "selective growth advantage" within their environment. This is essentially the same phenomenon that we call "natural selection", albeit in a microscopic scale. Given the fact that cell division is responsible for most mutations, it is not surprising that the most common cancers arise from cells that divide frequently in the performance of their function. The origin of these cancers, then, is "genetic" because it lies in the malfunction of genes that control growth and survival, but these cancers are considered to be "sporadic" (that is, they are largely independent of heritable risk factors).

Cancer risk can be inherited. Mutations that contribute to cancer can also be inherited. An inherited mutation in a single gene that is important in cell growth control will increase the risk of that individual to develop cancer. This can be due to reducing the overall number of acquired mutations that must accumulate before a cell becomes cancerous, or it can be due to disabling a critical safeguard gene that normally prevents cells from becoming tumors. In humans, it is estimated that approximately 5% of cancers occur in people who have known heritable risk factors. In dogs, there appears to be a predisposition among certain breeds or families to develop specific types of cancer, suggesting that a hereditary component may be important in the

development or progression of the disease. However, the existence of heritable cancer syndromes in dogs remains to be conclusively proven.

How is cancer kept at bay? Although both heritable factors and behavioral factors are known that increase the risk of cancer in people, similar information for dogs is limited. We know, for example, that neutering has a protective effect on hormone related cancers (mammary cancer and prostate cancer) and this information has been used extensively to reduce the prevalence of these tumors in the non-breeding population of pet dogs. But little is known regarding specific factors that influence the risks for other cancers. Nevertheless, it is fortunate that dogs (like other higher vertebrates) have developed many built-in safeguards which mandate that abnormal cells be destroyed. For that reason, before cancer can take hold, a malignant cell must eliminate or evade these safeguards. Despite the alarming incidence of cancer in older dogs, the reliability of these systems is evident in the fact that many of our pets do not develop cancer until they reach an advanced age if at all.

Lymphoma (cancer of the lymph glands) and osteosarcoma (bone cancer) are among the tumors that are commonly seen in dogs. Lymphoma accounts for approximately 20% of all canine tumors, and >80% of cancers originating from blood cells. Most of the time, lymphoma appears as “swollen glands” (lymph nodes) that can be seen or felt under the neck, in front of the shoulders, or behind the knee. Occasionally, lymphoma can affect lymph nodes that are not visible or palpable from outside the body, such as those inside the chest or in the abdomen. In these cases, dogs may accumulate fluid in the chest that makes breathing difficult, or they may have digestive problems (diarrhea, vomiting, or painful abdomen). If left untreated, dogs with

lymphoma will generally succumb to the disease within 3 to 4 weeks. Treatment with prednisone (a corticosteroid) alone generally can induce rapid, but short-lived remissions (usually less than 6 to 8 weeks), and frequently renders the disease resistant to further treatment. Durable remissions are achievable in lymphoma, so the disease is generally considered to be “treatable.” Multi-agent chemotherapy, which is the standard of care for this disease, will induce remissions of 12 to 18 months in many cases. However, there are various subtypes of lymphoma that exhibit different behaviors, and some of the more aggressive types are unresponsive to any available treatment. For example, the median survival for dogs with lymphoma originating from B cells treated with multi-agent chemotherapy is approximately 14 months, whereas the median survival for dogs with lymphoma originating from T cells treated with multi-agent chemotherapy is approximately 6 months. However, there remains a lot of variability in the responses seen even when tumors are classified into these subtypes.

Osteosarcoma accounts for 85% of skeletal cancers. Large and giant breed dogs are at highest risk for developing osteosarcoma, possibly due to the fact that bone cells at the growth plates must divide many times to create the very long bones that are characteristic in these breeds. However, there probably are additional risk factors, which have yet to be defined. Osteosarcomas generally occur in the limbs, however, these tumors can arise anywhere in the long bones, as well as in flat bones (ribs, skull, and spine). Osteosarcoma is always a life-threatening disease because it is highly metastatic, making treatment of this type of cancer especially difficult. The standard of care for osteosarcoma of the limbs includes amputation or limb-sparing surgery, followed by adjuvant chemotherapy. The median survival for dogs with osteosarcoma treated with surgery

alone is approximately 100 days. The addition of chemotherapy (usually doxorubicin or a “platinum” drug) to the treatment regimen increases the median survival to >300 days. Various factors can be used to predict response to therapy, including the anatomic location and size of the tumor and serum alkaline phosphatase concentrations. However, there are no truly robust predictors of response, and the survival of dogs with osteosarcoma treated with standard of care can range from weeks to years.

What can we do to prevent and treat cancer? There are several breed clubs and animal health organizations, including the AKC Canine Health Foundation that are supporting research projects that will help define cancer risk factors for dogs, and also to develop rational new treatment strategies to improve the outcome of cancer patients. The AKC Canine Health Foundation recently launched a “Cancer Initiative” to raise almost one million dollars to support cancer research projects. These projects seek to define markers of heritable cancer risk, identify markers that improve the ability of veterinarians to predict responses to standard, available treatments, and develop new strategies for therapy based on known genetic anomalies peculiar to tumors. The research project “*Heritable and Sporadic Genetic Lesions in Canine Lymphoma and Osteosarcoma*” (AKC CHF Grant 2254) is a collaborative effort between Dr. Jaime Modiano at the AMC Cancer Research Center in Denver, CO and Dr. Matthew Breen at North Carolina State University in Raleigh, NC that seeks to determine how genes impact the development of cancer in dogs. Specifically, the researchers will study abnormalities in genes and chromosomes in lymphoma and osteosarcoma to determine if these abnormalities are inherited, and to assess their clinical significance (that is, if they are predictive regarding response to treatment and prognosis).

In the short term (few years), this study may help identify “genetic pawprints” in tumors that can be used to predict if they are likely to respond to conventional therapy, allowing owners of affected dogs to make more informed decisions regarding treatment for their pets. In the long term, we anticipate that this and other studies may define specific gene markers that define cancer risk for individuals and their progeny that can be used for judicious breeding decisions to reduce the incidence of cancer in dogs.

Your assistance is essential to the success of these projects. Your generous donations to your breed club’s Health Fund and to the AKC Canine Health Foundation will help support worthwhile research projects that will help us understand, prevent, and treat cancer in our dogs. As important, we urge to you look at the accompanying solicitation for participants, and if you know of a dog that is eligible to participate (or a dog that were unfortunate enough to become eligible), we request that you contact the health representative for your breed or the investigators for additional information. With your help, we will improve the health and well-being of our dogs!