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INTRATHORACIC NEOPLASIA: EPIDEMIOLOGY AND ETIOLOGY

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INTRODUCTION

Neoplasms of the thorax encompass those derived from the thoracic wall, trachea, mediastinum, lungs and pleura. They represent a wide variety of lesions including benign and malignant tumors arising from many tissues. The large surface area, 60 to 90 m^2 in man, represented by the respiratory epithelium and associated thoracic structures are ideal targets for carcinogens carried by inspired air. Very little is known regarding the epidemiology, etiology, and mechanisms of spontaneous intrathoracic neoplasia in animals. Much of what we know or suspect about thoracic neoplasia in animals has been extrapolated from experimentally-induced neoplasms.

EPIDEMIOLOGY

Unlike their human counterparts in which intrathoracic neoplasia, particularly lung cancer, is a major cause of death, intrathoracic neoplasia in domestic animals is an unusual cause of death. Primary pulmonary neoplasms are uncommon in dogs, cats, and horses, representing approximately 1% of all neoplasms in these species. An often cited incidence rate for respiratory tract tumors is 8.5/100,000 dogs and 5.5/100,000 cats. The prevalence of primary lung tumors is 4.17 cases/100,000 dogs, according to one study. Although an increase in the number of primary lung tumors in dogs over the last 20 years has been reported. It appears to be a disease of middle age with most tumors occurring during the second decade of life. There is limited evidence to implicate environment or owner occupation as factors in the development of intrathoracic neoplasia in animals.

GEOGRAPHIC VARIATIONS

Few studies have attempted to link the distribution of canine respiratory neoplasms to environmental distribution. In one study, the environment was divided into urban and rural areas based on atmospheric pollution and industrialization concentration around a major metropolitan area. While no significant differences were noted in the patient distribution between urban and rural areas for respiratory tract cancer in that study, it shouldn't rule out the potential usefulness of animals as comparative models for environmental health or for being at risk along with human subjects.

GENETIC AND INTRINSIC FACTORS

Genetic and intrinsic factors have been implicated in the pathogenesis of intrathoracic neoplasia. For example, pre-existing skeletal abnormalites such as multiple exostoses or osteochondromas in man have reportedly progressed to chondrosarcomas, whereas malignant transformation to both chondrosarcoma and osteosarcoma has been reported in the dog and cat. Familial aggregation of OS has been described in St. Bernards. Specific breed predispositions for neoplasms occurring within the thoracic cavity inlcude: (1) thyroid carcinoma in boxers, golden retrievers, and beagles; (2) neoplasms

of the chemoreceptor system in certain brachycephalic breeds (boxer, Boston terrier); and (3) cardiac hemangiosarcomas in German shepherd dogs. There is no apparent sex predilection.

VARIATIONS IN PATHOLOGIC TYPE

It has been hypothesized that cancer risk can be related to some etiologic agents by studying the distribution of cell type. For example, in man certain well-identified industrial agents produce lung cancers with an alteration of the usual cell type or location. The chloromethyl ethers and exposure to ionizing radiation produce predominately oat cell carcinomas. Alterations by location are noted with asbestos, which generally produces tumors in the lower lobe and peripherally, and with exposure to chromates, which results in an equal distribution of upper and lower lobe cancers. A recent study that examined the histologic cell type, doubling-time, and distribution of radiation-induced lung cancers in beagle dogs, failed to identify any significant differences between those cancers and spontaneous neoplasms.

ETIOLOGY

In contrast to human subjects, where smoking is clearly the single biggest cause of respiratory tract neoplasia, few risk factors have been clearly defined in domestic animals that can be pointed to as primary causes of intrathoracic carcinogenesis. There are, however, several factors that have been implicated as etiologic agents in both spontaneous and experimentally-induced disease.

IONIZING RADIATION

Radiation has been clearly associated with cancer of the thoracic cavity. Most of what we know about lung cancer in domestic animals has come from experiments utilizing dogs exposed to various types of ionizing radiation. The principle goal of those studies was to demonstrate the essential safety of certain types of radiation exposure, and establish dose-response relationships. Lung cancer has been induced in dogs using a variety of internally-deposited fission-product radionuclides including plutonium, cesium, yttrium, cerium, strontium, and americium. External exposures using whole-body X- and gamma-irradiation, fast-neutron and photon irradiation have also produced lung cancer in the dog. Extensive studies have also been conducted in dogs on the biological effects of inhaled radon daughters. Lung cancers were produced at similar radiation dose levels as those encountered by uranium miners. Although initially directed toward the problems of uranium miners, these studies may be of even greater benefit and interest in relation to general population risks from radon daughter exposures related to non-occupational exposures such as those encountered by living in tighter, more-energy-efficient housing, or by proximity to mine tailings piles. It is certainly conceivable that, in this environment, animals could be equally at risk along with man for radon-related pulmonary disease.

CHEMICALS

Lung cancer can be induced by a wide variety of vapors, dusts, and aerosols. These can be divided into three general classes: organic chemicals;

inorganic chemicals; and complex mixtures. Most experimental carcinogenesis studies employing chemical agents have concentrated on two types of compounds - polycyclic aromatic hydrocarbons, especially benzo(a)pyrene, and nitrosamine, particularly diethylnitrosamine. Many of these compounds are extremely toxic and carcinogenic. They also bind the soluable Ah receptor and are thereby capable of inducing cytochrome P-450IA1 through expression of CYP1A1 gene. Cytochrome P-450IA1-dependent aryl hydrocarbon hydroxylase (AHH) activity, in turn, plays a central role in metabolism of these chemicals to their ultimate carcinogenic derivatives. These reactive derivatives bind to DNA, forming DNA adducts, which lead to DNA damage often in the form of point mutations. Individuals with genetically higher levels of AHH activity, or altered CYP1A1 gene expression, may be at increased risk for carcinogen-induced cancer in the human population.

VIRUSES

Among the so-called oncogenic viruses, retroviruses have been most commonly associated with neoplasms of the thoracic cavity in domestic animals. The anterior mediastinal form of feline-leukemia virus (FeLV) induced malignant lymphoma in cats is the most frequently encountered intrathoracic neoplasm identified in the species, while the thymic (adolescent) form of bovine leukemia virus induced bovine lymphoma is sporadically reported. Pulmonary adenomatosis of sheep is a spontaneous, contagious lung tumor that has also been associated with a retrovirus infection.

ENVIRONMENTAL AND OCCUPATIONAL CAUSES

A retrospective study has shown a statistically significant association between mesothelioma in dogs and an asbestos-related occupation or hobby of a household member. There was also a significant association between mesothelioma and the use of flea repellants. Although asbestos exposure can induce bronchiogenic carcinoma, mesothelioma, and pulmonary fibrosis, the molecular mechanism responsible for the toxicity and carcinogenicity of asbestos remains unknown. Two recent reviews have suggested that the iron content in asbestos may be responsible for the biochemical and biological effects of asbestos. The most carcinogenic forms of asbestos contain iron to levels as high as 36% by weight and catalyze many of the same biochemical reactions that freshly prepared solutions of iron do, such as the formation of oxygen radicals, lipid peroxidation, and DNA damage.

Although smoking is one vice that people have been unable to transfer to domestic animals, lung cancer has been experimentally induced in dogs by exposure to cigarette smoke or carcinogens derived from smoke. With evidence from recent studies suggesting that passive smoking may subject nonsmokers to greater risk for lung cancer, it is possible that, as animals live longer, the relative risk for developing lung cancer related to tobacco products or co-carcinogens to those products will increase.

MECHANISMS OF CARCINOGENESIS

Carcinogenesis involves a complex interplay of heredity and environment. If there is a unifying principle, it is that carcinogenesis is a multistage process. Most experimental and epidemiological data are consistent with a two-stage model for the pathogenesis of cancer. This view is supported by the

classical initiation-promotion experiments of Berenblum and Shubik, the occurance of tumors in two forms, one not inherited and the other inherited in an autosomally dominant fashion, and the observation that in hereditary neoplasms the inheritance of the gene is not sufficient at the cellular level to give rise to cancer. According to the two-stage model, the first mutational event leads to an improperly controlled proliferation of cells that have sustained that event. After the second event has occurred, the cell is committed to developing into a clinically apparent cancer. Despite the importance of the steps that lead to cancer, until recently neither the number of steps nor their nature was known for any neoplasm.

Recent advances in molecular biology have allowed the elucidation of the molecular events involved in the development of solid tumors. These techniques have demonstrated that these neoplasms develop by a stepwise accumulation of several mutations, some of which activate oncogenes that push cells toward the cancerous state while others inactivate genes that suppress tumor growth (tumor suppressor genes, anti-oncogenes). This stepwise progression has been most clearly demonstrated for colon cancer in man, but it may represent a model of genetic carcinogenesis applicable to many neoplasms regardless of site of origin. This series of genetic changes includes: point mutations, chromosomal rearrangements and deletions, gene amplification, and changes in gene expression. The target genes include dominant acting cellular oncogenes, putative recessive genes uncovered by deletions, and genes for growth factor and/or their receptors especially the so-called autocrine growth factors produced by the cancer cells themselves.

Radiation-induced and spontaneous lung cancers in the beagle dog have been studied in order to identify the number and nature of the specific cellular changes involved in the stepwise progression of normal cells to neoplasia. Available data appears to fit the two-stage model. Radiation produces DNA strand breaks and chromosomal aberrations consistent with deficient DNA repair and activation of proto-oncogenes to active oncogenes by deletion, translocation, or other gross chromosomal rearrangement. There is a strong association between inflammation, proliferation, and subsequent carcinogenesis. Studies with tumor tissue, taken from both radiation-induced and spontaneous tumors, have shown that the DNA contained tumor-specific restriction fragment-length polymorphisms associated with H-ras, K-ras, erb B, src, v-ros, c-met, and myc genes. Normal homologues for some of these genes are receptors for growth factors, and deregulation of these genes may play a major role in growth regulation (proliferation) of these cells. Another important mechanism by which cell growth may be deregulated is through the conversion of various growth factors and/or their receptors to oncogenes. These factors can stimulate or inhibit cell proliferation by paracrine or autocrine pathways, and overexpression of these factors may confer a proliferative advantage to initiated or neoplastic cells. Epidermal growth factor receptor (EGFR), epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), insulin growth factor-1 (IGF-1), and bombesin appear to be overexpressed in both radiation-induced and spontaneous lung tumors in beagle dogs. However, the significance and time-course of these molecular mechanisms in the genesis of thoracic neoplasia is still unclear at present. The processes and results described point out the complexity of these diseases, but they also suggest a model for carcinogenesis in domestic animals and provide some guideposts pointing to future research possibilities in veterinary oncology.

References available upon request.

Key words: Carcinogenesis, respiratory, epidemiology, genes

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