

Genetic Impact of Disease Risk: Understanding Prevention & Treatment

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We can confidently state that the genetic basis of cancer is now beyond question. It is estimated that at least five mutational events are required for overt malignant transformation, and genomic instability seems to be necessary to establish a self-renewing population of cells (possibly cancer stem cells) whose progeny expand to cause clinical disease. Ultimately, a subpopulation endowed with metastatic properties that is drug resistant leads to death of the cancer patient. A major focus of contemporary cancer genetics is to define whether such properties are inherent to cancer stem cells or whether they arise by natural selection and clonal evolution.

Cancer is the leading cause of death in humans under the age of 85, as well as the leading cause of disease-related death in dogs; thus, it holds exceptional importance in our society. Both genetic and environmental factors have major effects on the temporal occurrence of cancer, and there is a new emphasis to learn more about how these factors influence cellular and molecular changes in cancer. Dogs and people are susceptible to similar types of cancer with comparable natural histories (incidence, age of onset, location, progression, outcome). Pet dogs share our environment closely, allowing us to examine not only the heritable risk factors, but also those associated with the environment. Furthermore, when compared to humans, dogs have shorter generational life spans (as many as five or more related generations frequently co-exist), extended pedigrees with detailed family histories, and more homogeneous genetic backgrounds, which provide unique opportunities to address questions about the origin and behavior of cancer. The answers we obtain studying cancers of dogs will contribute to our ultimate goals to design strategies for prevention and treatment of cancer in both dogs and people.

To understand the implications of cancer, one must first realize that cancer is not a simple disease. Rather, "cancer" describes a large number of diseases whose only common feature is uncontrolled cell growth and proliferation. A very important concept that is now universally accepted is that "cancer is a genetic disease, although it is not always heritable." Tumors arise from cells that accumulate mutations which eliminate normal constraints of proliferation and genetic integrity. These mutations provide cells a selective

growth advantage within their environment by essentially the same evolutionary phenomenon that we call "natural selection", albeit on a microscopic scale. Various theories have been proposed to explain the genetic basis of cancer. One invokes stochastic (random) events--the inherent error rate of enzymes that control DNA replication introduces about 1 in 1,000,000 to 1 in 10,000,000 mutations for each base that is replicated during each round of cell division. The genome consists of millions of base pairs, so each daughter cell is likely to carry at least a few mutations in its DNA. In other words, the single most important risk factor for cancer is life...Most of these mutations are silent (they do not present problems to the cell's ability to function), but others can disable tumor suppressor genes or activate proto-oncogenes that respectively inhibit or promote cell division and survival. An alternative hypothesis is that mutations are not stochastic, but rather "directed" due to the presence of a "mutator phenotype," where the factors that control DNA replication and repair are inherently prone to more errors than would be expected by simple stochastic events in particular individuals. This leads to different cancer predispositions, which would be higher than the mean in such individuals, and might explain why not all people (or dogs) exposed to similar environmental carcinogens develop the same forms cancer at the same rate. There is evidence to support both mechanisms (stochastic and directed) in people and animals.

Various types of cancer syndromes have been identified in dogs, including a heritable cancer syndrome associated with a mutant tumor suppressor gene (renal cystadenoma and nodular dermatofibrosis of German Shepherd Dogs) characterized by Ostrander and Ligaas; several cancer syndromes with significant heritable influence, such as bladder cancer in Scottish Terriers described by Knapp, Glickman, and others; cancer syndromes that are mediated by somatic mutations like mast cell cancer due to mutations of c-Kit reported by London and colleagues; and cancer syndromes strongly associated with environmental factors and oncogenes, including mammary cancer as shown by Dorn and others.

An approach that has been successfully used to identify genes that contribute to human cancer is the study of recurrent chromosomal abnormalities. Major technical obstacles that hindered comparable work in dogs were overcome by the work of Breen and colleagues. Since, our groups have documented breed specific prevalence (and hence, presumed patterns of inheritance) for canine non-Hodgkin lymphoma (NHL). As importantly, we have shown that pathognomonic molecular abnormalities of both NHL and

leukemias of dogs and humans are conserved, indicating the underlying basis for these diseases is firmly embedded in the genome and may result from peculiar aspects of mammalian evolution.

Current knowledge and available molecular tools allow us to predict prognosis and response to therapy in some cancers of companion animals, and we believe the availability and usefulness of such tools in clinical practice will expand rapidly. As we improve our understanding of fundamental mechanisms that account for malignant transformation and tumor progression, we will be able to design even better strategies for cancer prevention and therapy.