

## **Understanding Cancer at the Breed Level**

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“Cancer has become a public disease in humans, but we haven’t broken the silence about cancer in dogs, and it is still considered a very private matter for some breeders,” Rhonda Hovan said.

Using Golden Retrievers as a model, she explained the importance of using survey data to understand how cancer affects a specific breed. For example, 60% of Golden Retrievers will die from cancer, but the average lifespan is still approximately 11 years, similar to other like-sized breeds. Certain cancers also appear to be more prevalent, including hemangiosarcoma (HSA) and lymphoma.

“Cancer is not a single disease, but many diseases that share certain characteristics,” Hovan said.

Gathering accurate statistics on the disease is complicated, she said, because many owners report cancer by the location the tumor is found. Hemangiosarcoma (HSA) tumors, for example, can be found anywhere in the body because cancer cells can circulate throughout the bloodstream to other organs. No matter where the tumor is found, however, if the tumor cells are epithelial cells, then it can be accurately reported as HSA.

When cancer is suspected, Hovan recommended that breeders request pathology to get an accurate diagnosis, consider necropsy to determine the cause of death, and wait to report the disease until pathology or necropsy reports confirm the findings.

Cancer is a genetic disease, Hovan said, but it is not necessarily inherited. This is because genes are found in two kinds of cells: germ—both sperm and egg—cells, which affect the next generation, and somatic cells, which do not. Cancer is caused by mutations, or errors, in genes. Mutations can be found in either germ or somatic cells.

Most cancer in dogs is at least partially inherited. Even with mutations in a sperm or egg, however, Hovan said a puppy might not get cancer. A cell must go through many stages before it becomes cancerous. Puppies may be predisposed, but there are more factors that affect their chances of developing the disease.

Environmental risk factors, which can be random mutations, advance the dog a few more steps along the pathway to cancer. However, age appears to be the single, greatest risk factor for the disease.

“Any animal that is past its natural age of reproduction is at increased risk for cancer,” Hovan said.

Although animals have inherited mechanisms that favor good health, this theory of natural selection holds true only through the animal's ancestral age of reproduction, which for dogs is about five to seven years. This is one of the reasons scientists consider cancer a natural part of the aging process, she said, and why cancer is rare in young animals.

Once a dog passes its natural age of reproduction, cancers that occur are often sporadic varieties that may be the result of unlucky mutations, and have no identifiable, inherited cause. Most cancers in dogs and humans are this kind.

Data collected on cancer in Golden Retrievers show the breed's gene pool is widely divergent and its cancer rates are elevated worldwide. Immune-mediated diseases such as hypothyroidism and allergies also are higher than average. Since cancer rates tend to increase when the immune system is compromised, immune-mediated diseases could signal increased cancer risk.

The breed's high rate of cancer, predominance of specific cancers, and high rate of immune-mediated diseases, taken together, indicates an inherited disposition for cancer in Golden Retrievers. Should this be true, Hovan said, the potential to reduce cancer risk through breeding should be examined.

This endeavor requires identified lines within the breed that have more or less cancer risk. No such lines exist within the Golden Retriever population, she said. If there are no dogs with a lower risk, there also are no available genes to mediate the gene pool.

Breeding in a longer lifespan might appear to be a way to extend the age of the dog before it gets cancer; however, this solution does not seem to work with any degree of consistency. The difference between dogs with middle-age-onset cancer and those with late-onset cancer—or those who may never get cancer—usually has more to do with random mutations and the environment than with heritable genes.

Although no good tools are available to help with breeding selection today, Hovan said studies are being funded by the CHF to identify genes associated with lower cancer risk.

In the meantime, modifying a dog's lifestyle, including keeping puppies and dogs lean and fit, can mitigate risk. Thin dogs have been shown to live more than two years longer than obese dogs, she said, and have a later age of onset for cancer. Supporting research indicates that feeding dietary supplements, including raw vegetables and fish oil, may reduce cancer risk. Limiting exposure to environmental factors linked to increased incidence of cancer, such as paints and solvents, asbestos, second-hand smoke, and certain herbicides is also helpful.

The link between cancer and other environmental factors such as x-rays is not as clear. Although fetal cells are most vulnerable to damage from x-rays, Hovan said, large lifetime studies of high-risk breeds exposed to standard doses of prenatal x-rays have not been done.

Age at neutering is another factor that can affect cancer risk. Breed-specific data collected on Golden Retrievers found that dogs neutered after one year of age lived longer than those neutered earlier. Again, Hovan said, the longer lifespan may translate into a later onset of the disease.

Scientists have recently learned that gene expression can be permanently modified prior to birth. A study with mice tested the theory by feeding pregnant females a diet supplemented with genistein, a soy protein. Their offspring had lower rates of diabetes, obesity, and cancer. However, breeding out disease in this fashion may have unintended consequences.

A similar situation occurred in 1976 when a research colony was formed in an attempt to eliminate hyperuricosuria, a sometimes-fatal disease in Dalmatians that causes stones to form in the urinary tract. The disease has a recessive mode of inheritance, but all Dalmatians have two copies of the disease allele. Since no Dalmatians have a normal copy of the disease allele, Hovan said, it was impossible to breed out the disease.

To get around this, researchers introduced a Pointer—believed to be a distant ancestral breed of Dalmatians—into the Dalmatian population. After five generations, the resulting offspring were approximately 97% Dalmatian and 3% Pointer, had normal alleles and no hyperuricosuria, and could be used to breed out the disease.

Unfortunately, she said, the dogs with the normal alleles always carried a spotting pattern that did not match the breed standard. It was discovered that the diseased allele was linked to correct Dalmatian spotting, and a choice was made to accept “stone forming” disease as part of what it means to be a Dalmatian.

Breeds, by definition, are closed gene pools, and therefore are under selection pressure to shrink. With each generation, Hovan said, desirable genes are selected for and less desirable genes are reduced or eliminated. Disease genes that are linked to desirable traits are selected for by default, and over generations become more common in the population.

Just as Dalmatian breeders had to decide whether to change the breed to reduce the risk of disease, others may be faced with similar challenges as more information is discovered about the link between DNA and disease. Hovan cautioned participants not to act hastily.

“As much as we are all going to eagerly await these new DNA tests that will tell us if our dogs are at risk or are not at risk for cancer, it may be healthier for our gene pools if we sort of sit back and let the whole picture emerge before these decisions are made.”

Hovan encouraged Parent Club members to donate samples from their affected dogs to help ongoing studies, and include that information on the Canine Health Information Center (CHIC) DNA Repository for future studies.

*Discussion*

A participant from the Afghan Hound Club of America asked when Golden Retrievers first come into season and the optimal age for sterilization. Hovan said Golden Retrievers first come into season near one year of age.

Another participant said more veterinary schools should encourage their students to do necropsies on dead dogs. She said it has been very difficult to convince veterinarians in her area to conduct necropsy on her dogs.

A participant questioned whether the fact that larger breeds age faster than smaller breeds was taken into account in the research. "Do cancer statistics go down for the breeds that age slower?" Hovan said she did not know, but that the topic bears further investigation.