



SCHOOL OF VETERINARY MEDICINE
CENTER FOR COMPANION ANIMAL HEALTH
UNIVERSITY OF CALIFORNIA
TELEPHONE: (530) 752-7295
FAX: (530) 752-7701

ONE SHIELDS AVENUE
DAVIS, CALIFORNIA 95616-8734

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Dear Friends of the CCAH:

Due to the impact that cancer can have on lives, we have dedicated the fall issue of *CCAH Update* to concentrate on this important topic. Although canine cancer is emphasized, this easy-to-understand pullout article applies equally to cancer in all of our animal friends and humans.

One-third to one-half of all animals, including humans, will die of cancer. Cancer is caused by the interaction of subtle differences in our regular genes (those inherited from Mom and Dad), as well as changes in our “ghost genes.”

Ghost genes can be altered during our lives by environmental factors, and some of these changes do not show up for one or more generations. The ghost genome is also known as the epigenome, and epigenetics is one of the newest and most exciting fields in science today. We hope that you find this review of cancer and its causes interesting and informative, whether or not you have lost pets of any type, family members or friends from this terrible disease.

The cancer program at the UC Davis School of Veterinary Medicine is rapidly expanding as a result of decisions made five years ago to make it a top priority. We have invested greatly in infrastructure, faculty and staff, and have linked our program to the UC Davis School of Medicine’s National Cancer Institute-accredited Cancer Center.

We greatly appreciate your support in the past and look forward to working with you in the future. We would not have come this far without our new building—the only building on campus constructed entirely from private donations.

Your support has also allowed us to fund faculty and resident research proposals on cancer in animals and to link our programs with those of the medical school. Our research has been entirely based on naturally occurring cancers seen in our veterinary oncology clinic patients.

In the spirit of “One Medicine,” researchers in the veterinary and medical school cancer centers aim to learn from each other. Trials being conducted with dogs have and will benefit people, and breakthroughs in human cancer treatment are likewise rapidly applied to our animal patients.

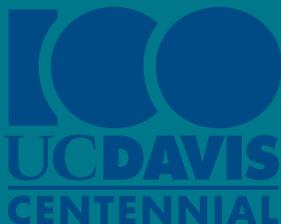
We have included a story about the personal experiences of Marley and his owners with cancer. Their story demonstrates the commonality of cancer and its emotional price.

We extend a personal invitation to you to visit our Veterinary Cancer Center and to see what we have accomplished and are accomplishing with your help.

Yours sincerely,

A handwritten signature in blue ink, appearing to read "Niels C. Pedersen".

Niels C. Pedersen, DVM, PhD
Director, Center for Companion Animal Health



UC Davis celebrates its 100th anniversary in 2008–09, and the School of Veterinary Medicine marks 60 years of accomplishments in animal, human and environmental health.

Marley's Story

A happier dog you'll never encounter. Marley dispelled the myth of being two seemingly disparate things—both human friendly and an American Pit Bull Terrier. Marley was strikingly handsome, bright, athletic, comical, rife with curiosity and possessed an extraordinary temperament. Life was great with Marley, our breed ambassador.

Saddled with allergy and skin issues from the time he was a puppy, Marley became a patient of the Dermatology Service at the UC Davis School of Veterinary Medicine when he was 18 months old. He quickly gained celebrity status with both students and veterinarians, who were entertained and amazed by his well-executed behaviors performed on command: “Stand” (he'd stand for the examination), “Side” (he'd lie on his side), and “Open” (he'd open his mouth). And then there was his famous “Freeze” (he'd freeze like a statue—momentarily broken with a tail wag).

We knew we were facing a lifetime of skin challenges, but we had no idea what was about to hit us. On a routine visit to UC Davis in January 2007, our world came crashing down after a student discovered swollen lymph nodes. Tests confirmed that Marley had stage V high-grade B-cell lymphoma—the highest stage possible.

Two days later we were in a UC Davis Center for Companion Animal Health oncology exam room where the veterinarians explained—very concisely and with compassion—that without treatment, Marley had six to eight weeks to live. And those would not be fun times.

We proceeded with chemotherapy, with Marley's celebrity status accompanying him, and his ardent admirers growing. Throughout his care, if you didn't know Marley had a life-threatening disease, you probably wouldn't have been able to tell. This is evidence of the oncology team's emphatic mantra: providing quality of life for the companion animals they treat.

While we were there for treatments, we observed the oncology team's interactions with other patients and came away knowing that every animal is treated as unique and special. Individualized, down-to-earth attention is foremost. They all truly care.

Ultimately, Marley's tenacious spirit, all our love, and the CCAH's best efforts were outgunned by the cancer. But because of their care, Marley enjoyed 15 additional months of quality living. With heartfelt gratitude to the CCAH team, we savored every precious moment.

Since we all stand on the shoulders of those who have gone before us, sharing information is crucial. In that spirit, some of Marley's tissues were donated to the CCAH for research. To honor and memorialize him, we purchased a brick and a plaque to be displayed in the CCAH gardens, with the proceeds supporting lymphoma research. Many friends and relatives touched by Marley's life and story have also made contributions in his name.



Marley, wearing his “doggles”

—Kirk and Charmaine Fornoff



Center for Companion Animal Health
UC Davis School of Veterinary Medicine

By learning more about canine cancer, owners may be able to assess whether their dog could be at risk, and what they might be able to do to reduce the chances that their dog will be affected.

About the Author

Rhonda Hovan has been a breeder and owner-handler of Golden Retrievers for more than 30 years. As a freelance writer, she has won both the Veterinary Information Network Health Education Award and the Eukanuba Canine Health Award.

Ms. Hovan is the research facilitator for the Golden Retriever Club of America and founded the Starlight Fund at the AKC Canine Health Foundation to support Golden Retriever health research. She also serves on the advisory board of the National Canine Cancer Foundation, and is an emeritus director of the Orthopedic Foundation for Animals. She lives in Akron, Ohio, with five Golden Retrievers and two rescued raccoons. She can be reached at RhondaHovan@aol.com.

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Special Report: Understanding Canine Cancer

By Rhonda Hovan

Just as it is in people, cancer is one of the leading causes of death in dogs. It's estimated that approximately one in three dogs will get cancer, which is very similar to the rate of cancer in humans. This increases to about one in two dogs over the age of ten. Clearly, cancer is a major concern to all who love and care for dogs.

Any dog can develop cancer, but some dogs are at greater risk of doing so than others. Sometimes this elevated risk is related to the breed of dog, and sometimes lifestyle factors can modify a dog's cancer risk. By learning more about canine cancer, owners may be able to assess whether their dog could be at risk, and what they might be able to do to reduce the chances that their dog will be affected.

Defining Cancer

First, it is important to understand that cancer is not a single disease, but many diseases that share certain characteristics. The predominant characteristics are that cancers contain cells that don't stop multiplying when they are supposed to and cells that don't die when they are supposed to.

Cancer can arise from many different types of cells, and its cell of origin gives a cancer its identity and unique characteristics. For example, one of the most common canine cancers, lymphoma (also called lymphosarcoma), arises in a type of white blood cell called a lymphocyte. A cancer that usually occurs in larger breeds, osteosarcoma, begins in bone cells; and as the name implies, mast cell tumors—common tumors that usually appear on the skin—arise from mast cells.

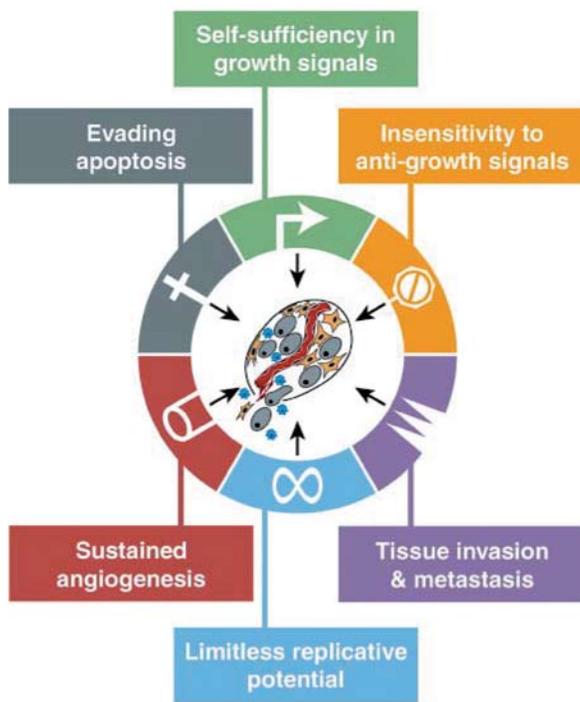
One cancer that is often confusing is hemangiosarcoma. This cancer forms from cells called endothelial cells that line blood vessels. Typically, hemangiosarcoma tumors form in very vascular organs such as the spleen, liver, right atrium of the heart, and lungs; but they can form in almost any organ, including the brain and skin. However, no matter where the primary tumor is found, it is not a "spleen cancer" or "liver cancer" or "lung cancer" if the tumor cells are endothelial cells. Attending veterinarians usually rely on a pathologist to examine cells from the tumor to identify the type of cancer.

Cancer as a Genetic Disease

So what causes a cancer to form? Veterinarians and scientists know that cancer is a genetic disease. But to dog owners and breeders, the word "genetic" does not necessarily mean the same thing that it means to cancer researchers. When scientists use the word genetic, they mean that they always need to look at genes to understand what has gone wrong to cause a cancer to form, because it is errors in genes that allow cells to multiply without normal controls.

But just because cancer is a genetic disease does not mean that it is strictly an inherited disease. So how can it be genetic and not be inherited? This is because genes are found in two kinds of cells, and one kind is inherited and the other kind is not. The kinds of genes most owners and breeders are used to considering are found in germ line cells, which are the sperm and the egg. These are the cells that contain genes that are passed on to the next generation. All other cells of the body are

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Acquired Capabilities of Cancer

For a normal cell to become a cancer, it must undergo the following changes:

- It no longer responds to all external signals that control its growth (self-sufficiency in growth signals)
- Ignores normal external signals to stop growing (insensitivity to anti-growth signals)
- It must be able to invade other tissues where it wouldn't normally grow (tissue invasion & metastasis)
- It becomes immortal (limitless replicative potential)
- It must be able to attract its own blood supply (sustained angiogenesis)
- It ignores signals telling it to commit suicide (evading apoptosis)

Figure 1. Modified from Hanahan & Weinberg, "The Hallmarks of Cancer," *Cell*, 100: 57–70, 2000 Elsevier, U.K.

called somatic cells. They also contain genes, but the genes in somatic cells are not passed forward and can have no effect on the next generation. Any mutations that might occur in somatic cells during the lifetime of the animal are confined to that one animal and cannot affect its offspring.

Every time a cell divides, it must make a copy of its genes for the new cell, and that copying process provides an opportunity for a mistake.

So errors in genes lead to cancers, and those errors are called mutations. Every time a cell divides, it must make a copy of its genes for the new cell, and that copying process provides an opportunity for a mistake. Most of the time, the mistakes are either corrected, eliminated or are harmless; but every now and then, a mistake that impairs

the normal function of a gene will be maintained. Fortunately, very few cancers are the result of a single mutation, and essentially all common cancers in dogs require numerous genetic errors. This is called the multiple hit theory of cancer (Knudson A, 1971), and applies to humans as well as dogs. It's estimated that cancers require at least five to six meaningful mutations to gain a foothold, and probably more.

These mutations can occur in germ line cells—the sperm and the egg—and they can occur in somatic cells. And it is most likely that the mutations leading to cancer come from a combination of germ line cells and somatic cells. Therefore, it is most accurate to say that cancer in dogs is partially inherited, and partially not inherited. Neither inheritance by itself nor environmental exposures by themselves cause cancer in dogs; but both contribute to cancer in dogs. Inherited mutations can be the first steps toward cancer, giving a puppy the predisposition to develop cancer—but the next steps occur during the life

of the dog, and are not influenced by heredity. This predisposition toward cancer certainly does not mean that cancer is inevitable, and many predisposed dogs will live long lives with no cancer.

The basic steps necessary for a cancer to grow are defined in the IPP model—initiation, promotion, and progression (Trosko JE, 2001). In the initiation phase, a cell is endowed with immortality or another growth or survival advantage, but is still held in check by its cellular environment. This step is particularly intriguing, because some very new research is pointing toward the strong possibility that this immortality can be an inherited component of cancer, and is part of the "cancer stem cell" theory. During the next step, promotion, additional mutations allow the cell to out-compete neighboring cells, and a tumor mass is formed. Finally, progression occurs when a third series of mutations leads to metastasis. Each of these steps is achieved through multiple mutations.

Figure 1, “Acquired Capabilities of Cancer,” shows the changes a normal cell must undergo to become a cancer.

Each one of these capabilities is abnormal for most cells, and one or more mutations must occur to endow the cell with each of these traits. Again, cancer is clearly not the result of a single event, exposure, or genetic cause; numerous things have to happen to result in a cancer.

Hopefully readers can begin to get the idea from this discussion that there will never be a single answer to the question of what causes cancer in dogs, or what will prevent cancer. It is more useful to think in terms of what contributes to the risk of cancer, and what might improve the odds of avoiding cancer.

Life is Risky Business

So of all the exposures that contribute to the risk of canine cancer, the greatest single risk factor is life. And the more of it a dog has, the higher the likelihood that a cancer will arise. This is because every time a cell divides, there is another chance for a mutation to occur. And since cells divide every day, each day that passes exposes a dog to one more day of risk.

This is certainly reflected in canine cancer statistics, because cancer is rare in young animals and becomes more common as they age. Further, the incidence of cancer in dogs rises significantly after the age at which its distant ancestors would have stopped reproducing. This is because over many thousands of years of evolution, natural selection favored animals that had genes most suited for survival, ensuring that genes for good health were passed to offspring. Likewise, animals with harmful genes weren't as successful at reproducing, so those genes were diminished in the population. But natural selection can only operate in animals prior to the end of their reproductive years, and once the natural age of reproduction is past, Nature has no stake in what happens to the individual. That is, if an animal got cancer at

7 years old, but was no longer reproducing anyway, then its cancer genes could not be eliminated via natural selection. Conversely, if an animal was especially resistant to cancer and was very long-lived, but was no longer reproducing into old age, then natural selection had no way to favor those desirable genes.

Therefore, through natural selection, animals have inherited mechanisms that favor good health—no cancer—only through the age at which thousands of generations of ancestors would have stopped reproducing. It is likely that for wild canine ancestors, that might have been around 5 to 7 years old, after which younger animals would have replaced them. This principle applies in all species, which is one of the reasons that cancers are uncommon among young humans and animals; and it is also one of the reasons that many scientists consider cancer to be a normal part of aging.

So very often, when a dog is past its ancestral reproductive age, what separates one with cancer from one without cancer are a few unlucky rolls of the dice—a few unlucky mutations. These random mutations result in what is known as sporadic cancer—that is, cancer that has no identifiable inherited cause. Most cancer in dogs, as most cancer in people, is considered to be sporadic cancer.

Breed Specific Risk

But not all breeds are created equal when it comes to cancer. Some breeds have less than the expected one-in-three incidence of cancer, and some breeds face much more grim odds. Breeds at elevated risk for cancer in general or certain specific cancers include Boxers, Bernese Mountain Dogs, Flat-Coated Retrievers, German Shepherd Dogs, Golden Retrievers, Rottweilers, and Scottish Terriers, among others (fig. 2).

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Type of Cancer

Breeds at Elevated Risk

Lymphoma
(Lymphosarcoma, LSA)

Boxer, Scottish Terrier, Basset Hound, Airedale Terrier, Chow Chow, German Shepherd Dog, Poodle, St. Bernard, Bulldog, Beagle, Rottweiler, Golden Retriever

Mast Cell Tumor (MCT)

Boxer, Bulldog, Basset Hound, Weimaraner, Boston Terrier, Golden Retriever, Labrador Retriever, Beagle, German Shorthaired Pointer, Scottish Terrier, Pug, Rhodesian Ridgeback

Hemangiosarcoma (HSA)

German Shepherd Dog, Golden Retriever, Flat-Coated Retriever, Boxer, Portuguese Water Dog

Osteosarcoma (OS)

Irish Wolfhound, Greyhound, German Shepherd Dog, Rottweiler, Great Dane, Scottish Deerhound, Great Pyrenees, Mastiff

Mammary Cancer

Poodle, Brittany, English Setter, Pointer, Fox Terrier, Boston Terrier, Cocker Spaniel, Lhasa Apso

Transitional Cell Carcinoma
(Bladder Cancer)

Shetland Sheepdog, Scottish Terrier, West Highland White Terrier, Beagle, Wirehaired Fox Terrier

Histiocytic Sarcoma
(including Malignant
Histiocytosis)

Bernese Mountain Dog, Flat-Coated Retriever, Golden Retriever, Rottweiler

Melanoma

Gordon Setter, Standard Schnauzer, Miniature Schnauzer, Doberman Pinscher, Scottish Terrier

Figure 2.

A breed predisposition toward certain specific cancers, or an increased incidence of cancer in general as compared to other breeds, are both evidence that there is an inherited component to cancer risk in those breeds. More evidence of an inherited contribution to some cancers comes from a recently published study showing that the two primary subdivisions of lymphoma, B-cell lymphoma and T-cell lymphoma, segregate along breed-specific lines (fig. 3).

Clearly, the possibility of an inherited predisposition to cancer is of great concern to breeders and owners of affected breeds, and several overlapping theories help to explain how such unfortunate situations may have arisen. A theory is an idea or principle that is developed to explain facts and observations, but until a theory can be proven, the theory itself is not a fact. The following theories have good supporting evidence, but they remain subject to revision as more data come in. Only finding actual genes involved in the

Some breeds report elevated rates of cancer wherever they are found around the world.

hereditary risk of cancer can provide definitive proof of the genetic mechanisms involved.

Some breeds report elevated rates of cancer wherever they are found around the world. This worldwide pattern suggests that these breeds were probably created from early founder dogs that carried genes that have been concen-

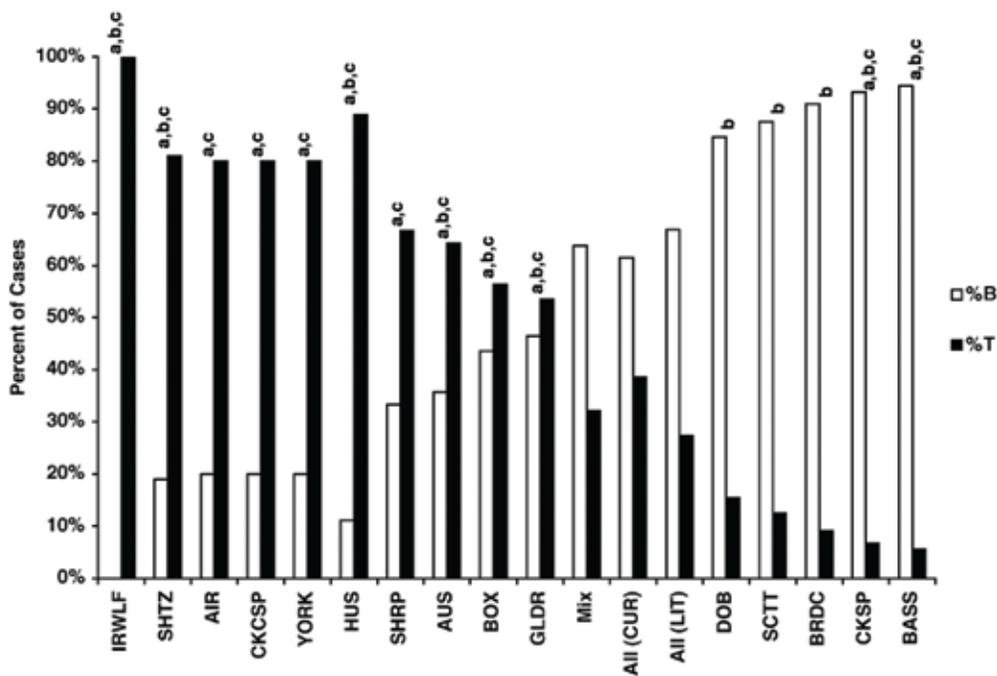


Figure 3. The frequency of B-cell (%B) and T-cell (%T) lymphomas in various pure breeds of dogs, as compared to mixed-breed dogs (Mix), total dogs in this current study [All(CUR)] and all dogs previously reported in the literature [All(LIT)]. Purebreds include Irish Wolfhound (IRWLF), Shih Tzu (SHTZ), Airedale Terrier (AIR), Cavalier King Charles Spaniel (CKCSP), Yorkshire Terrier (YORK), Siberian Husky (HUS), Chinese Shar-Pei (SHRP), Australian Shepherd (AUS), Boxer (BOX), Golden Retriever (GLDR), Doberman Pinscher (DOB), Scottish Terrier (SCTT), Border Collie (BRDC), Cocker Spaniel (CKSP) and Basset Hound (BASS). Statistical analysis by χ^2 : a=significantly different from mixed-breed dogs in current study; b=significantly different from total dogs in current study; c= significantly different from total dogs reported previously in literature.

Modified from Modiano, et al., *Cancer Res.*, 2005 Jul 1; 65(13): 5654–61.

trated over time (through an unintentional selection process that will be discussed later in this article), and which convey increased cancer risk throughout the breed today. An example of such a breed is the Golden Retriever, which has a cancer rate of about 60 percent, with hemangiosarcoma and lymphoma representing approximately one-half of the breed cancers.

A modified version of a founder effect can occur after a breed is already established if the breed undergoes a drastic reduction in population, and then rebounds using only the small number of remaining individuals to rebuild. This is called a population bottleneck, and the subsequent expanded population may become highly inbred. Since all dogs carry a mix of deleterious genes along with their desirable genes, this unavoidable inbreeding often results in some disease genes becoming more common in the breed.

Disease genes can increase in frequency in a breed... through the widespread breeding of popular sires.

Another way that disease genes can increase in frequency in a breed is through the widespread breeding of popular sires. Such sires may be highly prized because they exhibit many desirable traits, but less apparent deleterious genes are also present in every dog. Sometimes the influence of popular sires will be most noticeable within a certain segment of the breed's population, such as within one country but not all countries, or within lines bred for one type of competition but not all lines. In such instances, elevated rates of cancer may appear in a sector of the breed, while remaining at a normal level in other lines.

Further, some breeds that have a predisposition to cancer may also exhibit an increase in immune mediated disorders, including common diseases such as allergies, atopy and hypothyroidism. This is because a healthy immune system plays an important role in destroying abnormal cells before they have a

Some breeds that have a predisposition to cancer may also exhibit an increase in immune mediated disorders.

chance to cause disease. But a compromised immune system—in addition to causing immune mediated diseases—may also be ineffective in destroying cancer cells, and thus plays a pivotal role in allowing the progression of abnormal cells toward cancer. Therefore, a full evaluation of a dog's inherited cancer risk profile may need to include not only its breed, but also any clinical manifestations of immune disease.

Can Cancer Risk Be Reduced Through Selective Breeding?

Once they understand that some breeds are at increased risk for cancer, both breeders and owners are naturally interested in learning whether this risk can be reduced through selective breeding. Unfortunately, for most breeds that is not currently possible.

There are two significant obstacles to progress against cancer using breeding choices. First is that the cancer risk profile of most high-risk breeds developed as the breed developed, causing the entire breed to be at similar risk. This means that nearly all individuals in the breed share a common level of inherited risk, leaving breeders with no clear options to avoid risk-conferring genes.

Even when there might be differences in the level of inherited risk among

individuals in a breed, there are currently no tools that breeders can use to distinguish between dogs of high or low risk. Since there are not yet any genetic tests to identify genes that contribute to risk, breeders sometimes wonder if it would be helpful to try to select predominantly long-lived individuals to include in breeding programs. However, there are several reasons that this does not seem to be an effective strategy.

First, for dogs within the same breed, the difference between one that dies from cancer at 8 years old and one that lives to 12 is most often not under the control of inherited genes. The difference is more likely due to random lucky or unlucky mutations, or environmental exposures. In humans, the best data available indicate that inheritance accounts for only about one-third of longevity and the other two-thirds is environmental. There are no comparable data in dogs, but there is likely to be similarity. Although it may sound counter-intuitive, longevity in parents does not seem to be predictive for longevity in offspring. And while there are pedigrees in which individuals may appear long-lived for a couple generations, these are typically chance occurrences.

In addition, most pedigrees do not provide the depth of sibling data that is necessary to correctly evaluate complex traits in a family, and without this information about siblings, the full and accurate range of expression of the family genes cannot be known. (For a more complete discussion of sibling pedigree data, see "Collecting and Utilizing Phenotypic Data to Minimize Disease: A Breeder's Practical Guide" (<http://offa.org/hovanart.pdf>). An examination of the manner in which a familial risk of specific cancers is determined in humans will help to illustrate the complexity of interpreting pedigree data.

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Hereditary Nonpolyposis Colon Cancer (HNPCC)

All of the following criteria should be present:

At least 3 relatives must have cancer associated with HNPCC (colon, endometrial, ovarian, stomach, small bowel, hepatobiliary, ureter, renal-pelvis, brain)

One should be a first-degree relative of the other 2

At least 2 successive generations should be affected

At least 1 of the relatives with cancer associated with HNPCC should have received the diagnosis before age 50 years

Hereditary Breast/Ovarian Cancer

Any of the following criteria should be present:

Two breast cancers in a first- or second-degree relative and mean age at diagnosis of 40 years

One breast cancer and 1 ovarian cancer in a first- or second-degree relative and a mean age at diagnosis of 41 to 50 years

Two or more breast cancers and 1 ovarian cancer in a first- or second-degree relative

Ovarian cancer in 2 relatives

* Identified relatives for all of the above must be on the same side of the family (either maternal or paternal relatives)

Figure 4. Murff, et al., *JAMA* 2004 Sep 22/29; 292 (12): 1480-9.

Figure 4 provides guidelines that physicians use to determine whether members of a human pedigree are at risk for hereditary colon cancer or hereditary breast and ovarian cancer. Notice how very specific the criteria are, in numbers, ages, combinations and relationships. This specificity has been developed because physicians and researchers learned that simply identifying multiple affected relatives in a family was not accurate in predicting inherited risk.

But no such defined and detailed guidelines exist for breeders. While breeders and owners are understandably concerned when related dogs within a breeding line are affected with cancer, in high-risk breeds this kind of information is generally not useful in predicting inherited risk to relatives.

To further complicate attempts at pedigree risk assessment, cancer may not be the only disease that is increased in breeds with elevated inherited risk factors—immune mediated diseases

may be more frequent also. Although this is not known with certainty, it is possible that for some breeds, accurate assessment of the family's inherited cancer risk might also have to include relatives diagnosed with various manifestations of immune dysfunction.

For example, although these diseases may seem unrelated to cancer on the surface, dogs with immune mediated diseases such as hypothyroidism or atopy (a genetic tendency toward allergies) may actually have an inherited cancer risk profile that is very similar to that of dogs that have cancer. All in all, there is still too much unknown for breeders to make effective selections of dogs that have reduced inherited cancer risk or inherited longevity to include in breeding programs.

But although there are not currently tools to accurately guide breeding decisions, scientists are actively looking for genes that contribute to the inherited risk profiles of numerous cancers in many breeds. As these genes are found

and DNA tests developed, the goal is that breeders might be able to begin selecting dogs with a lower inherited risk to include in breeding programs. However, this might create an entirely new dilemma, and later this article will present a discussion of a breed that had the opportunity to eliminate a sometimes deadly disease, and the conflict surrounding that decision.

Effective Risk Reduction

Fortunately, there are some effective intervention strategies that may significantly improve a dog's cancer risk profile. Most important is to raise puppies to follow a very slow growth curve, and keep adults lean and fit. The data linking food restriction to reduced incidence of cancer and increased life span are well documented, and are supported not only by research in dogs (Kealy et al., 2002), but also in many other species, from humans to other primates to mice to worms. Although

the exact mechanisms aren't fully identified, it is thought that oxidation of food produces free-radicals, which cause DNA damage and inflammation, which are steps along the pathway to many diseases. Since cellular damage may take many years to fully manifest, and since cells are most susceptible to damage when they are rapidly dividing (such as during growth), it is thought that overfeeding during the earliest

Although maintaining lean weight is important throughout a dog's lifetime, there are two critical growth periods during which breeders and owners may wish to be particularly vigilant.

ages of puppyhood has the greatest potential for causing harm, including increasing the risk of cancer. The good news is that a dog's diet is totally under its owner's control, and has the potential to add more years of healthy life to dogs than any other known prevention strategy.

Although maintaining lean weight is important throughout a dog's lifetime, there are two critical growth periods during which breeders and owners may wish to be particularly vigilant. These are birth to 8 weeks, and 2 to 4 months. During these periods the goal should be growth that is steady but slow.

The rate of growth is directly determined by the amount of food that a puppy eats, so food should be restricted as necessary to keep puppies lean. Owners can determine healthy body weight by placing their fingertips on both sides of a dog's rib cage to assess the amount of skin and fat covering the ribs. The ribs should be very easily felt with little padding between the skin and the ribs. Puppies raised according to these guidelines will eventually achieve their full genetic height, bone and body conformation potential, although it will take them longer to do so than overfed puppies.

The lifelong benefits of following a slow-grow plan and keeping adults lean and fit may include reduced incidence and severity of orthopedic disease such as hip and elbow dysplasia, reduced incidence and later age of onset of cancers, and overall increased longevity.

There are also several dietary supplements that some research has suggested may possibly improve a dog's cancer risk profile. Recommendations include serving fresh cruciferous vegetables such as cauliflower, broccoli, Brussels sprouts, and cabbage approximately three times per week. Other research supports the daily addition of the omega-3 and omega-6 fatty acids found in fish oil (also called DHA and EPA), and there is some support for adding 200 mcg selenium and 400 I.U. vitamin E to the daily diet. Each of these acts as an anti-inflammatory and/or antioxidant, which counteract the inflammatory and oxidative effects of food.

At the same time as optimizing the good things that go into dogs, it is prudent to reduce their exposure to possible carcinogens. Environmental exposures that have been linked to an increased risk of cancer, and that can act as carcinogens by damaging DNA and/or increasing the DNA mutation rate, include coal or kerosene heaters, fumes from paints and solvents, asbestos, second-hand smoke, radiation, phenoxy herbicides and pesticides.

Specifically, exposure to coal or kerosene heaters, fumes from paints and solvents, and asbestos seem to be correlated with increased risk of several canine cancers. At this time, second-hand smoke has only been linked with nasal cancers in dogs, but evidence is mounting that there may be other associations too.

Radiation exposure—most commonly via x-rays—should be evaluated by balancing the benefit of improved diagnostics, when medically necessary, against the risk of harmful exposures, if less necessary. There is no precise number of exposures that is known to be fully safe, nor a certain number where harm begins. Rather, radiation damage is accumulative, and the greater the number of lifetime exposures, the greater the carcinogenic risk.

Also, in general, the younger in life that a dog is exposed to x-rays, the greater the risk, because rapidly dividing cells are most vulnerable to damage. As with many types of exposures, fetal cells are especially sensitive. Large lifetime studies of high-risk breeds exposed to standard doses of prenatal x-rays have not been done, but great care is taken to avoid prenatal radiation exposure in humans because this is known to be a significant cancer risk factor. Again, the balance of risk vs. benefit must be considered, and if a prenatal x-ray offers benefit that may save the life of one or more puppies (such as in determining that the litter is very large and that perhaps an elective C-section is advisable), then a prenatal x-ray may be a reasonable choice. However, it should be a thoughtful decision instead of a routine practice, especially in breeds already at high cancer risk.

Exposure to coal or kerosene heaters, fumes from paints and solvents, and asbestos seem to be correlated with increased risk of several canine cancers.

Herbicide and pesticide exposures are difficult to study, because use is so widespread that the true level of exposure is difficult to quantify. However, there are data implicating a link between exposure to a class of herbicides called "phenoxy herbicides" and certain canine cancers. These are fairly common chemicals used in yard care products. Since there are more than 1,100 names for various herbicides, owners can use the link www.alanwood.net/pesticides/ to enter chemical names from product labels to determine if a product is classified as a phenoxy herbicide.

Direct exposure to commonly used yard pesticides should probably be avoided, but this is not to be confused

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Cancer Therapies

Most canine cancers are first suspected when owners observe a change in their dog and present the dog to a general practice veterinarian. Depending on the specific findings of the history and physical examination, the veterinarian will usually need tests or procedures to determine the diagnosis. These can include blood and urine laboratory tests, x-rays, ultrasound, a needle aspirate to obtain cells, and a surgical procedure, among others. Usually when cells or tissues are obtained, they are sent to a pathologist for evaluation and diagnostic support.

Once the diagnosis is confirmed, owners face a number of decisions that sometimes must be made relatively quickly. One of the first decisions is whether to rely solely on the general practice veterinarian for treatment recommendations and ensuing care, or whether to consult with a specialist such as a board-certified veterinary oncologist. Just as most people facing a cancer diagnosis themselves or of a loved one seek the care of a physician oncologist, so may many dog owners wish to seek the specialized expertise of a veterinarian with advanced training and experience in treating cancer.

Depending on the kind of cancer, oncologists may have a number of different therapeutic approaches available to them. These might include surgery, chemotherapy, radiation and immunotherapy; and multiple therapies often are used in combination. For example, when a solid tumor is surgically accessible, typically it will be removed completely if possible, with care taken to include a margin of normal tissue around the tumor. Even when the tumor cannot be removed entirely, it is still important to remove as much as possible. This removal or reduction in size (debulking) is done near the beginning of the treatment plan because it reduces the number of cancer cells that may remain to cause recurrent or metastatic disease. In some cases, if the cancer has very low metastatic potential, and if the surgical margins show no evidence of disease, surgery alone may be curative. However, many cancers have a high likelihood of spreading, even after the tumor has been removed. And sometimes it is impossible to remove the entire tumor. In these cases, further therapy may be recommended to try to reduce or eliminate remaining cancer cells.

Oncologists may recommend following surgery with chemotherapy, radiation, immunotherapy or a combination of these. For many owners, the thought of chemotherapy brings to mind severe side effects they may be familiar with in some people who have undergone chemotherapy. Owners understandably don't want to do something that will cause their dog undue suffering. For this reason and others, chemotherapy protocols for dogs have been developed with quality-of-life concerns as a high priority. Chemotherapy side effects in dogs are usually manageable so that the dog is comfortable, happy and can live a reasonably normal life. Osteosarcoma and soft-tissue sarcomas are examples of cancers for which surgery followed by chemotherapy might be recommended.

Radiation therapy is another option for some cancers. Although it is sometimes used alone, radiation is most often used in combination with other therapies. Whereas chemotherapy is used to kill cancer cells throughout the body, radiation is narrowly focused and is used to kill cancer cells in a localized area. Therefore, the side effects also tend to be localized. Radiation may also be used to relieve symptoms of cancer by shrinking tumor size, even when achieving prolonged survival may not be realistic. Radiation administered as a comfort measure is called palliative therapy. Because dogs receiving radiation must remain motionless, they are briefly anesthetized during the procedure. Mast cell tumor is an example of a cancer that is sometimes treated with surgery first, followed by radiation, and sometimes chemotherapy too. An example of a tumor type that can respond to radiation used as palliative care is an osteosarcoma in which the tumor was not removed surgically (typically by amputation).

A type of cancer therapy that is currently of great interest to oncology researchers is immunotherapy. The premise of cancer immunotherapy is that the immune system has the ability to attack and eliminate cancer cells in much the same way that it attacks infectious agents. There are several approaches to enhancing the body's immune response to cancer, some of which are called targeted therapies because they are directed specifically at cancer cells and do not damage healthy cells. This specificity gives them the important advantage of causing few side effects, while sometimes achieving dramatic improvement. Cancer vaccines are a type of targeted therapy that teach the immune system to recognize and destroy cells from a certain tumor type. Recently a canine melanoma vaccine became the first cancer vaccine to receive USDA approval. It is important to understand that cancer vaccines do not prevent cancer in an unaffected dog, but rather are aimed at preventing a recurrence of a cancer that the dog already had. Canine melanoma is often treated with surgery first, followed by radiation and immunotherapy (vaccine).

Systemic cancers such as lymphoma are usually treated with chemotherapy, which is typically very successful in inducing temporary remission of the disease. Newer immunotherapies for lymphoma, including lymphoma vaccines, are under investigation.



Dusty, a Golden Retriever, is examined by resident veterinarian Steve Shaw and veterinary technician Virginia Cannan. Following amputation of the right rear limb due to osteosarcoma, Dusty continues to receive chemotherapy.

"Dogs who receive bone cancer surgery and chemotherapy live, on the average, one year. Twenty-five percent go on to live two years, and some are cured," says Dr. Katherine Skorupski, assistant professor of clinical medical oncology at the UC Davis School of Veterinary Medicine.

with monthly or “spot-on” flea and tick products. These products work in a way that does not appear to affect mammals, and there are strong safety data in mammals. In fact, a recently published study (Duncan et al., 2008) indicated that Golden Retrievers treated with monthly or spot-on products had a significantly reduced incidence of lymphoma, although the reasons for this are not yet clear.

Reduced incidence of testicular and mammary cancer have long been cited as important reasons to neuter dogs prior to 1 year of age, and it is true that spaying a bitch prior to a first heat cycle will ensure the lowest possible risk of mammary cancer. However, the incidence remains fairly low when spaying is delayed until after the first cycle, but before the second. For males, there is no difference in the rate of testicular cancer between males neutered prior to 1 year and those not neutered until 2 years of age. As recent research is raising important questions about the impact of early neutering on the risk of other cancers, a more complex picture is emerging.

For example, several recent studies have suggested a possibly improved overall cancer risk profile for dogs of both sexes that have been permitted to mature with their natural hormones. Some of this is still under investigation, and the associations may or may not be supported by future studies. But there are some data in Rottweilers, for example, that suggest that the risk of osteosarcoma decreases with every year that spaying or neutering is delayed (Cooley et al., 2002). Further, a study of over 1,200 cardiac hemangiosarcomas (Ware and Hopper, 1999) indicated a fivefold increase in hemangiosarcoma in spayed bitches as compared to intact bitches, and higher incidence in neutered males as compared to intact males. So questions are being raised for which the answers aren't in yet, but it's possible that neutering recommendations might ideally be tailored for different breeds, taking into consideration breed specific cancer risks.

Complex Interactions and Unintended Consequences

There is much interest among cancer researchers in an emerging field in genetics called epigenetics, which literally means “above genetics.” It's been known for many years that the information encoded in genes does not tell the whole story of how those genes are expressed over a lifetime. In fact, the ability to modify gene expression is the reason that the previous section on risk reduction can present effective

The information encoded in genes does not tell the whole story of how those genes are expressed over a lifetime.

cancer prevention strategies. Only very recently though have scientists begun to understand how gene expression can be permanently modified prior to birth.

The mice in figure 5 are essentially genetically identical—except that they don't look alike, and their differences go deeper than appearance. Obviously, the mice on the left are heavier and more gold, and the mice on the right are slimmer and darker. Despite the feeding regimen and all other lifestyle

factors being kept the same, the darker mice remain thinner and have lower rates of diabetes and cancer throughout their lives. The study that produced these mice was investigating a nutrient called genistein that is found in soybeans and is usually more abundant in Asian diets. Asians living in Asia have low rates of obesity, diabetes and cancer, but that advantage tends to disappear after one generation of living in the United States. It was long suspected that the diet and lifestyle of western cultures adopted by second generation Asian-Americans was the culprit. But these study investigators took one step backwards, and considered the prenatal environment. They supplemented pregnant mice with the same level of genistein typically found in Asian diets, and found that the offspring became not only darker in color (despite having exactly the same color genes), but were also more protected from obesity, diabetes and cancer. As more is learned, the concept of purposefully altering gene expression prior to birth could have tremendous power in helping to manage the risk of many diseases, perhaps including the risk of cancer in dogs.

Another fascinating aspect of this photo is the way it illustrates that two seemingly very different traits like coat

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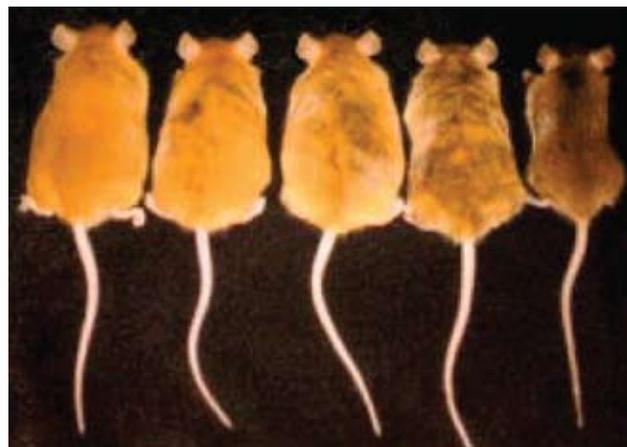


Figure 5. Dolinoy DC, et al., *Environ. Health Perspect.* 2006 Apr 114 (4): 567–72.

color and cancer can be linked. This could have surprising implications. For example, just as dog breeders of the past created breeds to meet certain descriptions (Standards), imagine that mouse breeders were creating a breed, and that the mouse Standard required a gold coat. It could happen that these mice breeders would keep selecting for gold coats—and feeding their pregnant mice a diet low in genistein—and the resulting mouse breed would have an elevated incidence of cancer. And if they had no idea that gold coats were linked to elevated rates of cancer, they might keep doing this generation after generation, and wondering why so many gold mice died from cancer.

Well, something similar actually happened in Dalmatians, which are at risk for a genetic disease called hyperuricosuria, or “stone forming disease.” Dogs

Dalmatians are at risk for a genetic disease called hyperuricosuria, or “stone forming disease.”

with hyperuricosuria have a metabolic defect that sometimes causes bladder stones to form, which, depending on the severity, can range from a manageable disease to a fatal disease. The gene responsible has been identified, and although it is a recessive disease, all Dalmatians have two copies of the disease allele (an allele is one-half of a gene pair, and each parent contributes one allele to its offspring), so all Dals have some form of the disease. And because there are no Dalmatians with a normal copy of the allele, it is impossible to breed this disease out.

In 1976 a research colony of Dalmatians was established, and an ancestral breed, the Pointer, was reintroduced. Using Pointers, a normal allele was introduced into the research colony and maintained in the gene pool for five generations of crossing back to Dalmatians. Since only one normal allele is necessary to produce

healthy dogs, they were able to produce healthy dogs that were about 97 percent Dalmatian, and three percent Pointer. At this point, the Dalmatian Club petitioned the American Kennel Club (AKC) to admit these dogs for registration, which was granted, and the breed then had normal genes to use to eliminate hyperuricosuria. Good success story, right? But that's not where it ends.

Unfortunately, it turned out that Dalmatians with the normal allele always had a less defined spotting pattern than was ideal. It was eventually shown that the disease causing allele was linked to correct Dalmatian spotting. After thoughtful but emotional debate of the question “Should a Dalmatian change its spots?” the Dalmatian Club asked AKC to rescind registration of the Pointer crosses, and essentially a decision was made to accept stone forming disease as “part of what it means to be a Dalmatian.” (But the cross-bred colony has been maintained, and research into this disease continues.)

Is it possible that breeds with a high risk of cancer could ever be faced with similar choices? Could some part of “what it means to be a certain breed” be linked with the risk of cancer? Unfortunately, this is a very real possibility. Remember the theories presented above that deleterious genes from founder dogs can concentrate over time to the point at which they can result in a breedwide elevated risk of cancer?

So what makes genes concentrate like that? Well, with every generation that goes by, breeders are constantly selecting desirable genes to keep in the gene pool, and less desirable genes to reduce or eliminate. Thus the gene pool of every breed is always under selection pressure to shrink, and as closed gene pools, they can never get any larger. The reason that breeders may have inadvertently kept and concentrated genes associated with cancer risk is that those harmful genes may very well be linked to genes

Unlike stone-forming disease—which is caused by a mutation in just one gene—there are probably quite a few genes associated with the risk of various canine cancers.

for traits they selected as ideal in the breed. Such traits could be integral to the desired appearance of the breed, the typical temperament of the breed or the function of the breed. Thus, in the admirable quest to preserve the “essence” of a breed, breeders may have unwittingly revealed a hidden dark side.

At this time, genes that increase the risk of cancer in specific breeds have not been identified (with one exception), so breeders have not yet been faced with choices that may in some cases be very difficult, as it was for Dalmatian breeders. However, as scientists begin to identify such cancer risk genes and DNA tests become available to breeders, the situation is likely to be quite different from the Dalmatian scenario.

Unlike stone-forming disease—which is caused by a mutation in just one gene—there are probably quite a few genes associated with the risk of various canine cancers. There are probably also many genes associated with protecting against cancer. As enough of these genes are identified, it will probably be found that every dog carries a complex mix of some genes that elevate risk and other genes that may offer some protection.

It's not going to be straightforward to understand how to use this information, because it's not going to be a simple case of one gene causing one disease. Especially early on, when perhaps the first couple of risk genes are identified, there may be a rush to avoid breeding dogs with those genes. But making severe decisions that result in

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Clinical Trials Lead to Improved Therapies

Many human cancers are today considered curable or very long-term diseases, but it is still true that most dogs diagnosed with cancer will die of their disease. Oncology researchers and clinicians are actively working to bring better therapies to dogs, and this process often involves clinical trials of drugs, protocols or procedures. Although extensive safety and efficacy testing often precedes such clinical testing, it is only through actual use in dogs with cancer that results of novel therapies can be fully assessed.

Clinical trials follow specific guidelines to meet rigorous scientific and ethical standards, and it is expected that results (regardless of the outcome) will be submitted for publication in a peer-reviewed journal. Most clinical trials are conducted at teaching hospitals associated with schools of veterinary medicine, although sometimes independent veterinary practices may be involved. Some trials recruit dogs from within a single treatment center, and others may involve dogs from a number of centers around the country—but all participating centers must follow the same guidelines to ensure uniformity.

Although the specifics will vary depending on many factors, there are a number of widely accepted study designs commonly employed in clinical trials. Many of these involve comparing results from two well-matched groups of dogs, where one group receives therapy that is considered to be high quality based on current evidence (standard-of-care therapy), and the other group receives the therapy under investigation. Or sometimes all study dogs will receive the standard-of-care therapy, but in addition, one-half of the dogs receive a novel drug while the other half receive a placebo. In some cases, all of the study dogs receive the novel therapy, and results are compared to outcomes of other therapies from previously published data.

There are several reasons that owners may wish to consider enrolling their dog in a clinical trial. Sometimes the prognosis using standard-of-care therapies is poor, and owners are willing to try something new because it offers a measure of hope. Other times there may be very promising preliminary data on the novel therapy, and owners consider it a wonderful opportunity for their dog to receive the new therapy. In some instances, owners may not be able to afford to treat their dog without financial assistance, and clinical trials sometimes assume a portion of the costs of treatment.

Regardless of the trial design, there are certain common practices that owners can expect to encounter. As part of the enrollment process, owners will be asked to sign a consent form. The consent form details the tests and procedures that will be performed, defines whether the owner or the study will be responsible for certain costs, discusses anticipated benefits and risks to the dog, and explains the owner's obligations. Owners should take the time to read the consent form and ask questions if there is any part that concerns them or is not clear. It is important that owners fully intend to comply with all parts of the study, because noncompliance or lack of follow-through hampers the ability of the researchers to obtain meaningful information to benefit dogs in the future.

Owners of dogs enrolled in clinical trials are usually very pleased with the care and attention the dogs receive. Although oncologists endeavor to provide the best care available to all of their clients, there is a special partnership formed when the dog is participating in research. Owners are usually encouraged to stay in close touch to resolve any questions or concerns during treatment, and asked to continue with follow-up visits beyond the treatment period.

In most instances, the best source of information about clinical trials for which a specific dog may be eligible is the nearest school of veterinary medicine. Internet searches can sometimes locate other trials, but if these are far away from the dog's geographic location, it is unlikely that the dog would be able to meet the usual participation requirement of regular appointments.

Although there are sometimes wonderful and very exciting results for dogs treated with a novel therapy as part of a clinical trial, most often progress against cancer moves in smaller steps. Regardless of their own dog's outcome, owners of dogs that have participated in a clinical trial usually feel a sense of satisfaction in knowing that their dog has contributed toward an improved outcome for other dogs.



Anna Szivek, resident veterinarian at the Cancer Clinic in the Center for Companion Animal Health, treats Oliver, a Scottish Terrier with bladder cancer, using chemotherapy. Scotties are one of the breeds that have a relatively higher risk of developing bladder cancer, lymphoma or melanoma (see figs. 2 and 3).

New insights into cancer in dogs as a model for cancer in people are beginning to drive ever increasing interest, effort, and funding toward canine cancer research.

eliminating a portion of a breed's gene pool may not be healthy for the breed either, because shrinking gene pools present their own—usually unforeseen—dangers. So as much as dog breeders and owners eagerly await the ability to DNA test for some cancer risk genes, it may be wise to move slowly in the beginning and allow a more comprehensive picture to emerge.

A Brighter Future

It's been 35 years since President Nixon declared "war on cancer" in 1973, and there has been incredible progress in the treatment and prevention of cancer in people. Progress against canine cancer has lagged behind, but new insights into cancer in dogs as a model for cancer in people are beginning to drive ever increasing interest, effort and funding toward canine cancer research. Unlike mice—which do not usually spontaneously get the same cancers as humans—dogs naturally get many of the same cancers that people do. Further, some of these cancers behave in dogs very much like cancers behave in people. Dogs also closely share the human environment, and may in some respects be sentinels for environmental exposures.

In addition, the canine genome was published in late 2005 (Lindblad-Toh et al., 2005), providing researchers with a genetic map that further accelerated progress in canine cancer research. Investigators appreciate the unique advantages of doing DNA research in populations that are within closed gene pools (purebred dogs) and therefore inbred to a degree. Another advantage is that it is often possible to study very large, multi-generational canine families that would be nearly impossible to find among humans. All of these factors make dogs an important model to help advance human cancer research, but the research also benefits dogs.

Canine cancer research is being done using pet dogs that continue to live with their owners, and the best interests of the dog are always a priority. Dogs with cancer receive treatment according to their owner's wishes, and many owners find comfort in being able to donate a blood sample or a tumor sample when surgery is performed in the normal course of treatment. In this way, their dog can leave a legacy of hope to help dogs of future generations.

Many AKC parent breed clubs (www.akc.org/index.cfm) actively support cancer research, both with monetary donations and through recruiting their members to provide biological samples. Two other major supporters of canine cancer research are the AKC Canine Health Foundation (www.akcchf.org/) and Morris Animal Foundation (www.morrisanimalfoundation.org/). Contributions for clinical cancer research in the School of Veterinary Medicine can be made through the CCAH (www.vetmed.ucdavis.edu/ccah).

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