PERSPECTIVES

by Rhonda Hovan

Understanding Cancer in Golden Retrievers

About forty years ago, my aunt was diagnosed with breast cancer. Back then, no one talked about breast cancer, as if there were some shame in the diagnosis. In fact, no one talked about cancer much at all – and when conversation was necessary, it was in hushed voices. Amazingly, the "C" word was actually withheld sometimes even from the patient. This was a time when cancer was a private family matter, not a community health issue.

Then in 1973, President Nixon declared "war on cancer," and a year later First Lady Betty Ford announced publicly that she had breast cancer. Those two events were pivotal in changing public attitudes toward cancer. For perhaps the first time, talk of cancer became acceptable, and the veil of shame was lifted. Those acts of breaking the silence helped to transform the fear of cancer into action, and represented the beginning of over thirty years of incredible progress against cancer in people.

But when I talk with breeders about cancer in Goldens, sometimes I get the feeling that we have not quite broken the silence about cancer in dogs. Some breeders and owners still consider it a private matter, and we have not yet fully turned the fear into action against this disease in our breed. But I think we are on the brink of making that leap, and I hope this column will help to bring this disease into the light of day, and to dispel the shame, secrecy, and finger-pointing that serves only to impede progress.

The Stats

Let's get started with some data of how cancer affects our breed. Approximately 60% of all Goldens will die from cancer. By gender, it's 57% of females and 66% of males. Human cancer is also skewed slightly toward males, so it's not surprising that dogs are too. For comparison, the rate of cancer in Goldens is just slightly less than double the rate of cancer in all dogs, which is estimated to be about one in three (and which actually is about the same as in humans). But even though our cancer rate is nearly double the all-breed average, it's important to keep in mind that the average lifespan of the breed is still within the same 10-11 year range as all breeds. Our two most common cancers are hemangiosarcoma, affecting about one in five Goldens; and lymphoma, affecting about one in eight Goldens. These two cancers represent about half of all the cancers in the breed.

But these are just numbers, and now let's bring them to life by adding faces. Here are ten Golden puppies. If these ten puppies represent an average Golden litter, let's imagine that we can look into their futures. The two babies in the lower left corner were very hard to choose between – aren't those faces just too cute? (Photo 1)

But on average, two puppies in a litter of ten will be lost to hemangiosarcoma, and it might be both of those. (Photo 2)

This little girl playing tug-of-war (the one on the left is the Golden) might be the one that gets lymphoma.

Each one of these puppies on the diagonal is pretty awesome – nice short back and hocks on the upper left; look at that face and bone in the middle; and this little guy on the lower right is bold and sassy – but with a cancer rate of 60%, all three would be lost to cancer in an average Golden litter. (Photo 3)

So… now you know why we need to talk about this. This is our current reality. (Photo 4)

But the future is not written in stone, and all of these puppies are still happy and healthy. We – every one of us – have the potential to contribute toward progress against these diseases so that this very empty picture with only four puppies remaining might not happen.

Actually, before we leave these photos, I want to point out one side note. The raccoon playing tug-of-war, Vger, died from hemangiosarcoma at seven years old. I wanted to mention that because I think we sometimes have a tendency to wonder why this horrible

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scourge is happening to our dogs, and we think they have somehow been singled out for these cancers. But the truth is, cancer is a fact of life. It affects essentially all animals (yes, sharks included), and any animal that has lived beyond its normal reproductive life (which for a raccoon is about four years), is at increased risk for cancer. We'll discuss that in greater detail below. (Photo 5)

Identifying Cancers

Now let's define some basic terminology. First, cancer is not a single disease, but rather many diseases that share certain characteristics. The predominant characteristics – what makes them a "cancer" – 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.

Cancers are identified by their cell of origin. For example, all hemangiosarcomas arise in cells called endothelial cells, which are the kind of cells that line blood vessels. Likewise, lymphoma arises in cells in the lymph system, osteosarcoma begins in bone cells, etc. This is an important concept for owners to understand, so we're going to go in a little more depth. In particular, the most common cancer in the breed, hemangiosarcoma, is sometimes confusing because it can appear in many different organs. 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. Unfortunately, some vets casually use incorrect terminology with owners, and it is the source of much misinformation. But accuracy in diagnosis is the beginning of any progress against cancer, so it's important for owners to request pathology to correctly identify the type of cancer, not just the location of the tumor.

Another way that hemangiosarcoma can be confusing is that frequently the only symptoms are sudden collapse and death, and sometimes there is an assumption that the cause was heart attack or stroke. However, since heart attack and stroke are rare in Goldens, and hemangiosarcoma is the most common cause of death, a better "guess" in those circumstances is hemangiosarcoma. But again, without a post mortem, there is no way to be certain. Fortunately, in the near future the diagnostic challenge this disease sometimes presents is going to change, because one of the researchers supported by GRCA and GRF has recently developed a blood test to diagnose hemangiosarcoma, and this should be available to your vets soon. This is an important and welcome advance, and many dogs will be spared having to undergo a surgical procedure to diagnose this disease.

Cancer as a Genetic Disease

One thing you will hear all scientists say about cancer is that it is a genetic disease. But to non-scientists – and particularly to 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 breeders are used to considering are found in germ line cells, which are the sperm and the eggs. These are the cells that contain genes that are passed on to the next generation. (It may help in remembering "germ line" cells by thinking of "germinating seeds" that sprout to grow the next generation.) All other cells of the body are 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 happen to somatic cells during the lifetime of the animal are confined to that one animal and cannot affect its offspring.

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 very few cancers are the result of a single mutation, and essentially all common cancers in Goldens require numerous genetic errors. This is called the "multiple hit" theory of cancer, and applies to humans as well as dogs. It is estimated that cancers require at least 5-6 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 Goldens is partially inherited, and partially not inherited. Neither inheritance by itself, nor environmental exposures by themselves, cause cancer in Goldens; but both contribute to cancer in Goldens. 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. 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 and clinical disease. Each of these steps is achieved through multiple mutations.

For a normal cell to become a cancer, it

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must achieve the following capabilities:

- it must be able to tell itself to multiply
- it must be able to defy outside signals to stop multiplying
- it must be able to invade other tissues where it wouldn't normally grow
- it must be able to replicate endlessly
- it must be able to commandeer its own blood supply
- it must be able to resist signals to commit suicide

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.

Because of the kinds of capabilities that a cell needs to become a cancer, it turns out that certain kinds of genes are most likely to be involved, and these kinds of genes are called tumor suppressor genes and oncogenes (or tumor promoter genes). When a tumor suppressor gene is deactivated, it may not be able to keep a cancer from growing; and when an oncogene is inappropriately activated, it may signal cells to keep growing when they should stop. In general, because they are usually recessively regulated, mutations in tumor suppressor genes are considered to be likely candidates implicated in an inherited risk of 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 our dogs, or what will prevent cancer. It's all about what contributes to the risk of cancer, and what might improve the odds.

Life is Risky Business

The greatest single cancer risk factor is life. And the more of it we or our dogs have, the higher the likelihood that a cancer will arise. Makes sense, right, because every time a cell divides, there is another chance for a mutation to occur. And since cells divide every day, every day we and our dogs are exposed to one more day of risk.

Here's a little more detail. I mentioned above that any animal which has lived beyond its normal reproductive years is at increased risk for cancer, and let's examine why this is. The basics of natural selection are well known: that animals having genes most suited for survival live to pass those good genes on to offspring; and animals with harmful genes aren't as successful at reproducing, so those genes are 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 gets cancer at seven years old, but is no longer reproducing anyway, then its cancer genes cannot be weeded out via natural selection. Conversely, if an animal is especially resistant to cancer and is very long-lived, but is no longer reproducing into old age, then natural selection has no way to favor those desirable genes.

Therefore, through natural selection, animals (including humans) 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 5-7 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 Golden is past its ancestral reproductive age, what separates one with cancer from a 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.

Cancer in Goldens

Now we're going to get more specific about Goldens. First, data show that cancer rates in Goldens are elevated around the world. While other countries may have a slightly different proportion of certain cancers – for example, in the US our most common Golden cancer is hemangiosarcoma, but in the UK, the most common Golden cancer is lymphoma – the overall incidence of cancer in Goldens is high in all countries. It doesn't seem to matter whether the line is US, Canadian, Australian, UK, Danish, etc – if it's a Golden, its cancer risk is elevated. For the most part, national breeding lines today are separated by oceans; and we certainly don't all provide the same environments for our dogs around the world. So what would explain this universal finding?

For the next several paragraphs, we're going to discuss theories that explain various cancer data in Goldens. 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 data, but they remain subject to revision as more data come in. Only finding actual genes involved in the hereditary risk of cancer can provide definitive proof one way or the other.

The leading theory to explain the breed-wide elevated incidence of cancer is that very early founder dogs in the breed carried genes that have concentrated over time, and which convey increased cancer risk to essentially all of today's Goldens. These dogs would have lived prior to the exportation of Goldens around the world, so these are not individuals that we could find in current pedigrees. Or more accurately, these founder dogs appear in essentially all Golden pedigrees, but are too far back for most of us to track.

The next piece of the cancer genetics puzzle in Goldens is that our breed is also at increased risk for several immune-mediated diseases such as allergies and hypothyroidism. In fact, the number one reason for Goldens to be taken to the vet is various manifestations of allergy and atopy, which includes frequent hot spots, food allergies, goopy ears (that's a medical term), orange toes, etc. And it turns out that these diseases are also found at higher than average rates in Goldens around the world. This is relevant to our discussion of cancer because the immune system plays an important role in destroying abnormal cells before they have a chance to cause a clinical cancer, and a compromised immune system often leads to cancer. Therefore, some have expanded the Founder Dog Theory to include that founder dogs also carried genes that have led to widespread immune system dysfunction in the breed, which contributes to our dogs' risk for cancer.

Now if this is true, what it means to those who might be trying to assess cancer risk in pedigrees, is that the various manifestations of a compromised immune system would have to be considered to be a component of the inherited cancer risk profile of the breed. In other words, several dogs may have a very similar germ line (inherited) risk profile, and one gets cancer, another becomes hypothyroid, another gets lots of hot spots, and another has food allergies – but the underlying genes that put them at risk for cancer and which are passed on to the next generation, may be very similar.

The next data to help us understand cancer in Goldens has

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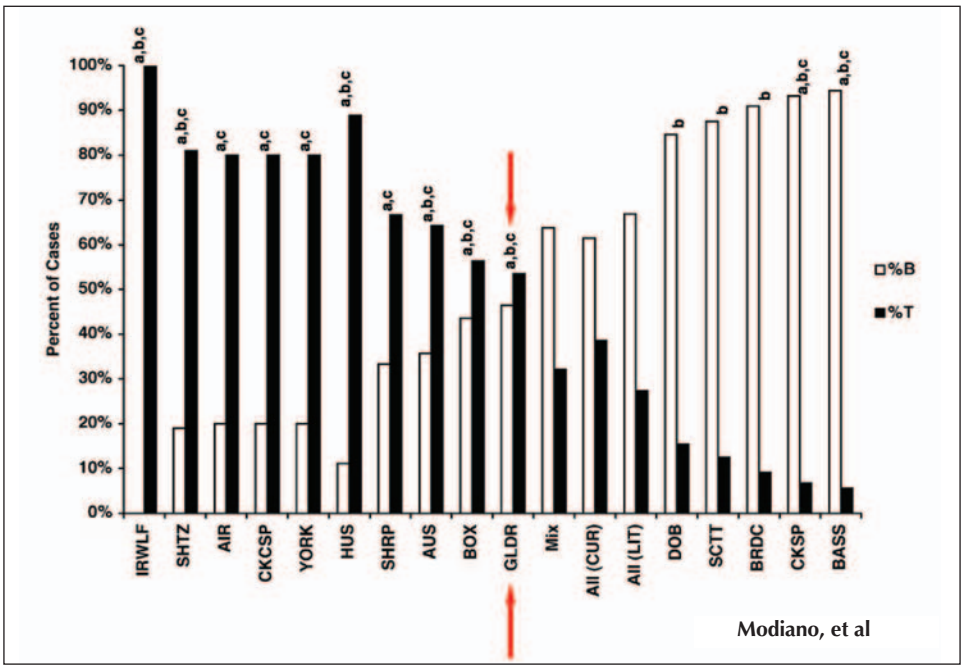
recently been published from research sponsored in part by GRF and GRCA. If you have ever had a Golden diagnosed with lymphoma, it is most likely that you were told only that your dog had lymphoma, but not a certain type of lymphoma (unless you participated in a research study). But there are two major subtypes of lymphoma, called B-cell and T-cell, and you can remember that by "B" for Bad and "T" for Terrible; as bad as B-cell disease is, T is usually worse. Overall, approximately 67% of canine lymphoma (all-breed) is B-cell and 23% is T-cell; but unfortunately, it turns out that Goldens get the short end of the stick there too, because most Golden lymphoma is T-cell. This information is so new that few general practice vets know it, and some oncologists may not even know it. But if your dog is diagnosed, it may be helpful that you know this data has been published, because it has the potential to impact treatment decisions.

And here's how it adds to what we know about inheritance of cancer risk. This chart shows that the B-cell/T-cell split in lymphoma is clearly breed specific, with some breeds heavily weighted toward one type of the disease or the other. Goldens are about 54% T-cell, and 46% B-cell. Further, these researchers also found that there are lines within our breed that are almost exclusively T-cell or B-cell.



That starts to give us a clue that not only is our breed as a whole at increased risk for cancer and other immune-mediated disease, but in addition, certain lines within the breed may have risks associated with specific cancers or subtypes of cancer.

More evidence for this line-specific risk profile comes from comparing UK data with US data. This shows us that while lymphoma is the most common cancer in UK Goldens, hemangiosarcoma is the most common cancer in US Goldens. In addition, UK Goldens appear to have more mast cell cancer than US Goldens. There is also some preliminary evidence that some US Golden lines may have an increased risk specifically of lymphoma or hemangiosarcoma, although this has not been verified yet.

Can We Reduce Risk Thru Breeding Decisions?

With these theories of cancer genetics for the breed in mind, one of the questions breeders always ask is "Can we reduce cancer through breeding decisions?" Unfortunately, the quick and dirty answer to that question is "Probably not at this time." But that's not a very satisfactory answer, so let's dig deeper. Going back to the theories of breed-wide elevated cancer risk and immune system dysfunction – the problem is that if pretty much all Goldens carry these defective genes – where do we go to get rid of them and bring in healthy genes? Still, the common logic is that if we keep breeding only dogs whose parents have been long-lived, and do that over and over, won't we be contributing those long-lived genes to the puppies and at least make some progress? But here's why that doesn't seem to work with any consistency.

First, the difference between the Golden that dies from cancer at 7 and the one that lives to 14 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 genetics accounts for only about 1/3 of longevity, and the other 2/3's is environment. There is no comparable data in dogs, but it is likely to be similar. Although this sounds counter-intuitive, longevity in parents does not seem to be predictive for longevity in offspring. Yes, there are pedigrees that will appear that way for a couple generations; but sometimes a chance roll of the dice will produce a "7" seven times in a row too. So while those things do happen, it does not mean those chance results have significance other than if enough rolls of the dice occur, someone gets lucky. Likewise, if enough examples are searched, a pedigree that appears especially long-lived can be found. Further, most pedigrees do not provide the complete sibling data that is necessary to accurately evaluate a family, and without this information about siblings, the full and accurate range of expression of the family genes is unknown. However, I really don't want to discourage breeders from trying if that is in their heart, but the data would lead more toward the conclusion that we just don't know enough yet of how to select dogs that may have true longevity in their genes.

But we did say that it appears that some specific cancers may be increased in certain lines or different countries, so can we use that information to reduce the risk of those specific cancers? To illustrate this task, and to further explain why sibling data is vital, let's examine how human medicine defines and detects a familial risk of specific cancers. Below are guidelines that physicians use to determine a human pedigree that is at risk for hereditary colon cancer and hereditary breast and ovarian cancer. Notice how very specific the criteria are, in numbers, ages, combinations, and relationship. This specificity has been developed because physicians and researchers learned that simply identifying multiple affected relatives in a family was not helpful in predicting genetic risk.

But no such defined and detailed guidelines exist for breeders. What breeders tend to do is note that (for example), "two grandparents died from cancer, and two of the aunts or uncles died from cancer, and the father's brother died from cancer" and conclude from that tally that the line is at risk. Unfortunately, in a breed with a 60% death rate from cancer, such information is just not helpful in predicting genetic risk. In fact, in pedigrees where enough information is known and available, this is normal for this breed. But again, as

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)*

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

with the longevity discussion, I don't want to discourage breeders from being conscious of cancer data in the lines they are breeding. There are no formulas or scientific guidelines to help you, but if you are uncomfortable with the cancer data from specific pedigrees, then you certainly can avoid those pedigrees.

So although right now we don't have good tools to guide our breeding decisions, several of the research projects that GRCA and GRF are supporting are investigating exactly these issues. In fact, those of you who allowed your dogs to provide blood samples to DNA drives at recent National and local Specialties are participating in these studies, among others. Especially with regard to our most common cancers, hemangiosarcoma and lymphoma, scientists are actively looking for genes that contribute to the inherited risk profile of Golden Retrievers. As these genes are found and DNA tests developed, the goal is that we might be able to begin selecting dogs with a lower genetic risk to include in breeding programs. However, this might present us with an entirely new dilemma, and later in this column we'll discuss how another breed had the opportunity to eliminate a sometimes deadly disease, and the dilemma that presented for them.

Effective Risk Reduction

Fortunately, we do have choices that may significantly improve our dogs' cancer risk profile. Most important is to raise puppies to follow a very slow growth curve, and keep adults lean and fit. The data are incredibly strong on this point, and come from not only research in dogs, but also 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. Put in simple terms, we rust. And the more food we eat over a lifetime, the more we rust. Since cellular damage may take many years to fully manifest, and since cells are most susceptible to damage when they are most rapidly dividing (which is during growth), it is thought that overfeeding during the earliest ages of puppyhood has the greatest potential for causing harm, including increasing the risk of cancer. So this factor – totally under human control – has the potential to add more years of healthy life to our dogs than any other known factor.

Below are age-specific Slow-Grow weight guidelines that are applicable to all Goldens, regardless of projected adult size or bone. 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, reduced incidence and later age of onset of cancers, and overall increased longevity.

Birth	1 wk	2 wks	3 wks	4 wks	5 wks	6 wks	7 wks	8 wks	10 wks	12 wks	16 wks	20 wks
1 lb	2 lbs	3 lbs	4 lbs	5 lbs	6 lbs	7 lbs	8 lbs	9.5 lbs	12 lbs	15-16 lbs	22-23 lbs	28-30 lbs

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 oxidation effects of food discussed above.

At the same time that we want to optimize the good things that go into our dogs, we also want to reduce their exposure to possible carcinogens. The following environmental exposures have been linked with an increased risk of cancer, and can act as carcinogens by damaging DNA and/or increasing the DNA mutation rate:

- Coal or kerosene heaters
- Fumes from paints and solvents
- Asbestos
- Second-hand smoke
- Radiation
- Phenoxy herbicides
- 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 the dog is exposed to x-rays, the greater the risk. As we discussed with regard to feeding, this is because rapidly dividing cells are most vulnerable to damage, and cells with DNA mutations early in life have more years to accumulate all of the further changes that are necessary for a cancer to grow (remember, it's not a one-step process). And as with many types of exposures, fetal cells are at especially high risk. So while there is not strong data in dogs implicating prenatal x-rays (sometimes done to count puppies) as increasing the risk of cancer, there is such data in humans, where great care is usually taken to avoid prenatal exposure. But 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 should be considered), then a prenatal x-ray may be a reasonable choice.

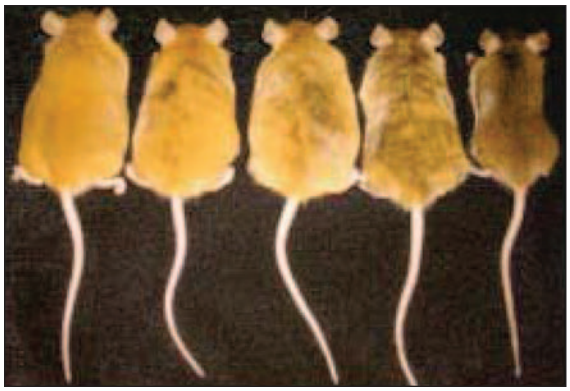
Herbicide and pesticide exposures are difficult to study, because there are so many of them and the level of exposure is difficult to quantify. However, there is data implicating exposure to a class of herbicides called "phenoxy herbicides" as linked to certain canine cancers. These are fairly common chemicals used in yard care products, but since there are over 1100 names for various herbicides, owners can use the link *www.alanwood.net/pesticides/* to enter chemical names from the product label to determine if the 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 with "spot-on" flea and tick products. The spot-on products work in a way that does not appear to affect mammals, and safety data in mammals is very strong. In fact, data from the GRF/GRCA Health Survey showed that Goldens treated with spot-on products have a significantly reduced incidence of both lymphoma and hemangiosarcoma, our two most common cancers. The reasons for this are not clear yet, although that is one of the areas currently under investigation by a GRF sponsored study.

There are widespread health considerations related to the age of neutering, but this column will focus on only those that impact the risk of cancer. Reduced risk of testicular cancer and mammary cancer have long been cited as important reasons to neuter dogs prior to six months of age, but those two cancers are only part of how the cancer picture is altered by altering a young puppy. Although many competition owners do not neuter their own dogs as puppies because they are potential conformation and/or breeding dogs, this discussion may pertain to breeders' requirements or recommendations for pet puppies sold on spay/neuter contracts.

It is true that spaying a bitch prior to a first heat cycle will ensure the lowest possible risk of mammary cancer. However, the risk remains fairly low when the spay 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 one year and those not neutered until two years of age. In humans, children with undescended testicles through at least two years of age do not face any increased risk of testicular cancer, but it might be prudent to neuter a dog with one or more abdominal testicles closer to one year than two years. In addition, 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 data is considered preliminary, and the associations may or may not be supported by future studies. But there is some data that suggests that the risk of osteosarcoma decreases with every year that the spay or neuter is delayed. Another study, of over 1200 cardiac hemangiosarcomas, indicated between a 2.4 times and 5 times increased risk of cardiac hemangiosarcoma in neutered dogs as compared to intact dogs (males and females). Since hemangiosarcoma is the most common cancer in the breed, this data might influence some owners to consider at least delaying neutering beyond early puppyhood. In addition, the risk of prostate cancer is also higher in neutered dogs than in intact dogs. However, this is not a common cancer, and it should be noted that the risk of benign prostatic hyperplasia (BPH, or enlarged prostate) is increased in intact males. But while BPH is about four times more common than prostate cancer in dogs, neutering after diagnosis is usually curative.

Complex Interactions and Unintended Consequences

The photo below (from Dolinoy DC et al, Environ Health Perspect. 2006 Apr;114(4):567-72) is incredibly fascinating, and represents an emerging field in genetics, called "epigenetics" which literally means "above genetics." We've all known for years that the information encoded in genes does not tell the whole story of how those genes are expressed over a lifetime – and a major example in human cancer is that we know smoking can damage genes and cause cancer in susceptible individuals. Only very recently though have scientists begun to understand how genes can be permanently modified prior to birth. The mice in this photo 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 same feeding regimen and all other lifestyle factors 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 lower rates of obesity, diabetes, and cancer, but that advantage tends to disappear after one generation of living in the US. It was long suspected that the diet and lifestyle of western cultures adopted by second generation Asian-Americans was the culprit. But this study 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 protected from obesity, diabetes, and cancer.



Wow, isn't that an amazing concept – maybe permanently reducing the rate of obesity, diabetes, and cancer – by altering diet during pregnancy? I so wish this research was further along, but it

will probably be many canine generations from now before this trickles down to dogs. Sure is tempting to feed my next pregnant bitch tofu though…

Another really interesting thing about this photo is the way it illustrates that two seemingly very different traits like coat color and cancer, can be linked. This could have surprising implications. For example, say you were a mouse breeder, and the mouse Standard called for a gold coat, so you kept selecting for gold coats (and feeding your pregnant mice a typical western diet), and your resulting mouse breed had an elevated incidence of cancer. But maybe you had no idea that gold coats were linked to elevated rates of cancer, so you kept doing it generation after generation, wondering why so many gold mice died from cancer.

Well, something similar actually happened in Dalmatians. Dals are at risk for a genetic disease called hyperuricosuria, or "stone forming disease." They have a defect in their metabolism that sometimes causes kidney stones to form, and depending on the severity, can range from a manageable disease to a fatal disease. This gene has been identified, and although it is a recessive disease, it turns out that all Dalmatians have two copies of the disease allele, 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.

Then 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 was maintained in the gene pool for five generations of crossing back to Dalmatians. Since only one normal allele was necessary to produce healthy dogs, they were able to produce healthy dogs that were about 97% Dalmatian, and 3% Pointer. At this point, the Dalmatian Club petitioned AKC to admit these dogs for registration, which was granted, and the breed now had normal genes to use to eliminate stone formers. Good success story, right? But that's not where it ends.

It seems there was a problem. Despite everyone's best intentions, it turns out that Dalmatians with the normal allele always had a less defined spotting pattern than was ideal, and in fact, it was eventually shown that the disease causing allele was linked to correct Dalmatian spotting. After much debate, 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."

Is it possible that we could ever face similar choices in Goldens? Could some part of "what it means to be a Golden" be linked with the risk of cancer? Unfortunately, this is a very real possibility. Remember the theories presented above that deleterious genes from early founder dogs have concentrated over time, to the point now where it has resulted in an elevated risk of cancer and a compromised immune system? 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. So in essence, the gene pool is always under selection pressure to shrink, and as a closed gene pool, it can never get larger. And one of the reasons that we may have inadvertently kept and concentrated genes associated with cancer risk and immune dysfunction is that those genes may very well be linked to genes that we have selected as part of what it means to be a Golden.

Here's a possible hypothetical example. While there is no research specifically linking genes for height to cancer, what is known is that shorter Goldens live longer than taller Goldens. In females the gain as they move from tallest to shortest is just over 1 year, and in males it's a whopping 2.2 years. In a breed whose males live an average of 10.7 years, that's a 20% increase. Selecting for shorter Goldens has the potential to raise the average longevity for both sexes to close to 13 yrs old. So the question is, what's it worth to us? Would we, or should we, ever consider changing the height Standard if it would mean increasing breed longevity? (This does not reflect my personal point of view, and is only discussed here as an illustration.) Interesting, isn't it, how considering such a question as it pertains to our own breed, suddenly changes the perspective of the question that was asked of another breed: Should a Dalmatian change its spots?

The Future Is What We Make It

Everything discussed in this article, everything that is known, and all that we still need to learn – is driven by financial support, and the amazing owners who donate blood and tumor samples from their affected dogs. Each issue of the GRNews contains a Cancer Sample Donation Chart, and the Chart along with an accompanying Letter to Vets can be downloaded from the GRCA website (*http://grca.org/health/ cancerdonation.pdf*) I urge you to print these and give them your vet, and request that the Chart be placed in your dog's chart for immediate access in an emergency. There's contact info for several research studies on the chart, and please also feel free to contact me directly; I know that sometimes it just helps to walk with someone who's been down the path.

I also want assure owners that privacy will be protected and information about their dog will be kept confidential if that is the owner's wish, with both dog identity and pedigrees coded for anonymity. Just a brief side note on that point though. Personally, I have always been very open about my own affected dogs, and one of the research studies once asked if I cared if my dog's name was used as the name of the line of cells that were grown from her hemangiosarcoma. I gave permission, and then forgot about it. Several months ago, and long after my sweet Frog had passed, I was reading a newly published paper and suddenly caught my breath when I unexpectedly started reading about "Frog" cells. I admit that I needed a moment to blink back tears, but when I was able to read again, I felt incredibly gratified that she had made a difference. I have felt that before with others of my dogs that have participated, and I truly believe that the vast majority of owners find that donating samples helps give meaning to their loss. As hard as it is to make that phone call or send that email offering samples in the midst of the shock of diagnosis and worry about your dog, it also offers lasting comfort to know that your dog didn't die in vain.

So I know you've heard it all before, and I really don't want to nag. Yet the sad fact is that only a small minority of GRCA members offer samples when their dogs are diagnosed. (And in my opinion, the ones who do step up to the plate deserve to be applauded as heroes.) But I dream of the day when everyone understands that we are all in this together, and that each of us has a personal responsibility to the breed we love to participate in cancer research.

I want to offer my personal thanks to all the researchers and oncologists who dedicate so much of their lives to trying to make progress against canine cancer; and especially to Jaime Modiano, VMD, PhD, for taking the time to answer my endless questions, and for reviewing my work for accuracy. Thank you also to the many organizations that support and fund this research, including CHF, GRF, GRCA, MAF, OFA, NCCF, and NIH, among others. And a special thank you to the unselfish owners who help make progress possible. ❖

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