Cancer

IMAGINE A 60-YEAR-OLD MAN recuperating at home after prostate cancer surgery, drawing comfort from the companionship of the aged Golden Retriever at his side. What the man probably does not realize, though, is that pet dogs like his could be important players in efforts to eliminate the suffering and death caused by cancer.

Dogs and humans often fall ill with the same kinds of cancers. Scientists contend that the similarities between these tumors, including genetic resemblances, can be instructive. (The background represents the DNA sequence from a tissue sample.)

Clues from Pet Dogs

Cancer studies in dogs can offer unique help in the fight against human malignancies while improving care for our pets

By David J. Waters and Kathleen Wildasin

Defeating cancer will require the application of everything in investigators' tool kits, including an openness to new ideas. Despite an unprecedented surge in researchers' understanding of what cancer cells can do, the translation of this knowledge into saving lives has been unacceptably slow. Investigators have discovered many drugs that cure artificially induced cancers in rodents, but when the substances move into human trials, they usually have rough sledding. The rodent models called on to mimic human cancers are just not measuring up. If we are going to beat cancer, we need a new path to progress.

Now consider these facts. More than a third of American households include dogs, and scientists estimate that some four million of these animals will be diagnosed with cancer this year. Pet dogs and humans are the only two species that naturally develop lethal prostate cancers. The type of breast cancer that affects pet dogs spreads preferentially to bones—just as it does in women. And the most frequent bone cancer of pet dogs, osteosarcoma, is the same cancer that strikes teenagers.

Researchers in the field of comparative oncology believe that such similarities offer a novel approach for combating the cancer problem. These investigators compare naturally occurring cancers in animals and in people—exploring their striking resemblances as well as their notable differences.

Right now comparative oncologists are enlisting pet dogs to tackle the very obstacles that stand in the way of achieving a cure for cancer. Among the issues on their minds are finding better treatments, deciding which doses of medicines will work best, identifying environmental factors that trigger cancer development, understanding why some individuals are resistant to malignancies and figuring out how to prevent cancer. Comparative oncologists ask, Why not transform the cancer toll in pet dogs from something that is only a sorrow today into a national resource, both for helping other pets and for aiding people?

WHY ROVER?

FOR DECADES scientists have tested the toxicity of new cancer agents on laboratory beagles before studying the compounds in humans. Comparative oncologists have good reason to think that pet dogs with naturally occurring cancers can likewise become good models for testing the antitumor punch delivered by promising treatments.

One reason has to do with the way human trials are conducted. Because of the need to ensure that the potential benefits of an experimental therapy outweigh the risks, researchers end up evaluating drugs with the deck stacked against success; they attempt to thrash bulky, advanced cancers that have failed previous treatment with other agents. In contrast, comparative oncologists can test new treatment ideas against early-stage cancers—delivering the drugs just as they would ultimately be used in people. When experimental drugs prove helpful in pets, researchers gain a leg up on choosing which therapies are most likely to aid human patients. So comparative oncologists are optimistic that their findings in dogs will be more predictive than rodent studies have been and will help expeditiously identify those agents that should (and should not) be tested in large-scale human trials.

Pet dogs can reveal much about human cancers in part because of the animals' tendency to become afflicted with the same types of malignancies that affect people. Examples abound. The most frequently diagnosed form of lymphoma affecting dogs mimics the medium- and high-grade B cell non-Hodgkin's lymphomas in people. Osteosarcoma, the most common bone cancer of large- and giant-breed dogs, closely resembles the osteosarcoma in teenagers in its skeletal location, aggressiveness and molecular changes. Under a microscope, cancer cells from a teenager with osteosarcoma are indistinguishable from a Golden Retriever's bone cancer cells. Bladder cancer, melanoma and mouth cancer are other examples plaguing both dog and master.

In a different kind of similarity, female dogs spayed before puberty are less prone to breast cancer than are their intact counterparts, much as women who have their ovaries removed, who begin to menstruate late or who go into menopause early have a reduced risk for breast cancer. But biology is teeming with trade-offs, and investigators are now recognizing that the biological factors that seem to protect women and dogs from breast cancer may come at the cost of accelerated aging and shortened longevity.

Canine cancers also mimic those of humans in another attribute—metastasis, the often life-threatening spread of cancer cells to distant sites throughout the body. Solving the mystery of how tumor cells metastasize to particular organs is a top research priority. When certain types of cancers spread to distant organs, they tend to go preferentially to some tissues over others, for reasons that are not entirely clear. Because metastasis is what accounts for most deaths from cancer, researchers would very much like to gain a better understanding of its controls. Studies in pet dogs with prostate or breast cancer might prove particularly useful in this effort because such tumors frequently spread in dogs as they do in humans—to the skeleton.

Scientists also have deeper theoretical grounds for thinking that pet dogs are reasonable models for human cancer. Evolutionary biologists note that

IN BRIEF

Millions of pet dogs will have cancer diagnosed this year. In many of those animals, the malignancy will look and behave much as it would in humans, such as spreading to the same organs. **Investigation of these cancers** can help researchers to better understand the biology of the human forms. Also, studies of experimental treatments in the animals can indicate which therapies most deserve further testing in dogs and humans and can offer guidance on the best doses and methods of delivery. **Such studies could lead** to progress in cancer prevention and therapy for both pets and people.

PRECEDING PAGES: ALISON KENDALL *(illustration)*; MEHAU KULYK *Science Source (DNA autoradiogram)*; THIS PAGE: JANA BRENNING *(dog tag)*

Breeds at Risk

The breeds represented by the dogs shown here are particularly susceptible to cancers that also afflict humans. These malignancies look like the human forms under a microscope and act similarly as well. Such resemblances mean that canine responses to experimental drugs should offer a good indication of how the compounds will work in humans. In addition, research into the genes that increase susceptibility of specific breeds to particular cancers is expected to help pinpoint susceptibility genes in humans.

Rottweiler:
Bone cancer

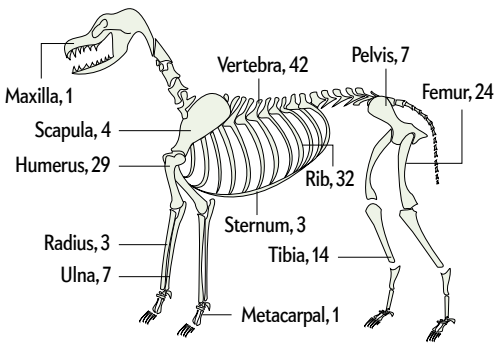
Collie:
Nasal cancer

Chow Chow:
Stomach cancer

Golden Retriever:
Lymphoma

Boxer:
Brain cancer

Scottish Terrier:
Bladder cancer



Skeletal distribution of metastases is another aspect of cancer similar in dogs and humans. In dogs, the lesions display the same "above the elbow, above the knee" pattern seen in people. Insights into why that pattern occurs in dogs could help explain the distribution in humans and perhaps suggest new ideas for intervening. (The numerals indicate the number of metastases found at each site in one study.)

dogs and humans are built like Indy race cars, with successful reproduction as the finish line. We are designed to win the race, but afterward it does not matter how rapidly we fall apart. This design makes us ill equipped to resist or repair the genetic damage that accumulates in our bodies. Eventually this damage can derange cells enough to result in cancer. In the distant past, our human ancestors did not routinely live long enough to become afflicted with age-related cancers. But advances in hygiene and medicine have rendered both longevity and cancer in old age common. Much the same is true for our pets. Pet dogs, whom we carefully protect from predation and disease, live longer than their wild ancestors did and so become prone to cancer in their later years. Thus, when it comes to a high lifetime risk for cancer, pets and people are very much in the same boat.

Aside from acquiring cancers that resemble those in people, pet dogs are valuable informants for other reasons. Compared with humans, they have compressed life spans, so scientists can more quickly determine whether a new prevention strategy or therapy has a good chance of improving human survival rates. Finally, although veterinarians today are far better equipped to treat cancer than they used to be, the standard treatments for the most aggressive canine tumors remain ineffective. Because of this, dog owners are often eager to enroll their animals in clinical trials that could save their pets' life—and possibly provide the necessary evidence to move a promising therapy to human clinical trials.

The Ideal Animal Model: An Invalid Concept

Some experts contend that progress toward finding cancer cures has been frustratingly slow because of the inadequacy of available animal models of human cancer. But perhaps the problem is not in the animals themselves but in the way they are used and what we are forcing them to tell us.

The dictionary defines a model as "an imitation." By definition, therefore, an animal model of cancer is not the same as a person who acquires cancer. Rodent models are often produced by making "instant cancers"—that is, by injecting the animals with tumor cells or bombarding them with carcinogen doses that are higher than any human will ever encounter. It is doubtful that cancers produced in that way will accurately recapitulate a complex process that often requires more than 20 to 30 years to develop in people. Naturally occurring animal tumors, such as those affecting pet dogs, provide the opportunity to study this complexity in a less artificial way.

But no one animal model is capable of answering all the important questions related to the prevention or treatment of a particular type of human cancer. Researchers would be best served by turning their attention toward carefully crafting specific questions and letting the questions drive the selection of the model system. For some questions, cell culture or rodent studies will be appropriate. To answer others, researchers will have to resort to studying humans. In that sense, a human clinical trial is a form of animal model research—a specific collection of individuals is being used to represent the overall human population. *—D.J.W.*

Rodents are a favorite model of cancer researchers, but therapies that work beautifully in rats and mice often fail in humans.

PASCAL GOETGHELUCK *Science Source*

ADVANCING CANCER THERAPY

VARIOUS CANCER treatment studies featuring pet dogs have now been carried out or begun. Some of the earliest work focused on saving the limbs of teenagers with bone cancer. Thirty years ago a diagnosis of osteosarcoma in a youngster meant amputation of the affected limb, ineffective or no chemotherapy (drugs administered into the bloodstream to attack tumors anywhere in the body), and almost certain death. Today limb amputation can be avoided by chiseling out the diseased bone tissue and replacing it with a bone graft and metal implant—a process partially perfected in pet dogs by Stephen Withrow and his colleagues at Colorado State University. Withrow's team pioneered technical advances that reduced the likelihood of complications, such as placing bone cement in the marrow space of the bone graft. The researchers also showed that preoperative chemotherapy delivered directly into an artery could convert an inoperable tumor into an operable one. The group's work is credited with significantly increasing the percentage of teenagers who today can be cured of osteosarcoma.

Although a tumor's local effects are often controllable using surgery or radiation, metastasis is much harder to combat. For that, drug therapy is required. New compounds under development aim to disrupt key cellular events that regulate the survival and proliferation of metastatic tumor deposits as well as their sensitivity to cancer-fighting drugs. For example, researchers are testing experimental agents that inhibit the formation of new blood vessels, which foster tumor growth and metastasis. Early trials in hu-

mans and dogs, conducted in parallel, can provide a deeper understanding of cancer-fighting mechanisms and help to identify the clinical settings in which these agents will be most effective.

Cancer researchers are also turning their attention to more familiar kinds of pharmaceuticals, including nonsteroidal anti-inflammatory drugs (NSAIDs), the class of compounds that includes ibuprofen. Certain NSAIDs have exhibited significant antitumor activity against a variety of canine tumors. In studies of pet dogs with bladder cancer, for example, the NSAID piroxicam showed such impressive antitumor activity that the results paved the way for human clinical trials of other NSAIDs (for example, the cyclooxygenase-2 inhibitor celecoxib) that can amplify the effects of conventional chemotherapy drugs.

Investigators have used pet dogs to study the intranasal delivery of a cytokine, a small immune system molecule, called interleukin-2 (IL-2) to treat naturally occurring lung cancers. Positive results from these experiments led to feasibility trials of inhaled IL-2 in human patients with lung metastases, further leading to trials with another immune cytokine, granulocyte colony stimulating factor. Researchers are hard at work optimizing species-specific immune assays and reagents so dogs can serve as a much needed model to advance other immuno-oncology applications in human cancer patients. Data from dogs will answer some of the central questions hampering the field of human cancer immunotherapy, such as who will likely achieve long-term benefit and which patients are most prone to adverse effects.

Researchers are also looking for the driver mutations within cancer cells that make a patient's tumor potentially lethal and difficult to treat. The work on human cancers revealed that the same sinister mutations can be operational in different types of cancer. This is leading to a reshuffling of cancer categories that extends beyond the conventional classification of cancers based on organ of origin. This approach has helped comparative oncologists discover an activating mutation in canine bladder cancers in a gene called *BRAF* that is identical to the mutation found in life-threatening human melanomas as well as cancers of the lung, thyroid and colon. This new thinking is paving the way for precision medicine approaches—the development of mutation-targeted therapies that could be effective in throttling cancers that arise in many different tissues of the body.

Another challenge that pet dogs are helping to overcome is determining the extent of tumor spread, referred to as clinical staging. Accurate staging is critical for devising therapeutic game plans that will maximally benefit the patient while minimizing exposure to harsh treatments that are unlikely to help at a given disease stage. For example, the odds that a teenager will survive osteosarcoma are increased by accurate identification and subsequent surgical removal of lung metastases.

Doctors typically determine the presence and extent of such metastases with noninvasive imaging techniques, such as computed tomography. To assess how accurate such scanning is, one of us (Waters), along with investigators at the Indiana University School of Medicine, collected CT images of the lungs from pet dogs with metastatic bone cancer and then examined the tissue at autopsy to verify that what was interpreted as a "tumor" on the scan really was a tumor and not a mistake. Results showed that state-of-the-art imaging with CT—the same type used in clinical staging of bone cancer in teenagers—significantly underestimates the number of cancer deposits within the lung. By revealing the limited accuracy of existing and experimental techniques, pet dogs are helping optimize the next generation of technologies for improved cancer detection.

TAKING AIM AT CANCER PREVENTION

BUT CANCER researchers are shooting for more than improved detection and better treatment; they also want to prevent the disease. Compared with treatment, prevention is a relatively new concept within the cancer research community. What cardiologists have known for a long time—that millions of lives can be saved through the prevention of heart disease—is gaining more traction in the cancer field. Although the term "chemoprevention" was coined almost 40 years ago to refer to the administration of compounds to prevent cancer, scientists did not gather nationally to debate cutting-edge knowledge of cancer prevention until October 2002.

Today the pace is quickening as investigators are examining a diverse armamentarium of potential cancer-protective agents. But finding the proper dose of promising agents has always been challenging. Indeed, failure to do so proved disastrous for some early human trials of preventives. For example, in two large lung cancer prevention trials, people receiving high doses of the antioxidant nutrient beta-carotene had an unexpected *increase* in lung cancer incidence compared with placebo-treated control subjects.

Can dogs accelerate progress in cancer prevention? Canine studies have already helped define the dose of an antioxidant—the trace mineral selenium—that minimizes cancer-causing genetic damage within the aging prostate. The message from the dogs: when it comes to taking dietary supplements such as sele-

JANA BRENNING

nium to reduce your cancer risk, *more of a good thing is not necessarily better.* Elderly dogs given moderate doses ended up with less DNA damage in their prostates than dogs given lower or higher amounts. Comparative oncologists hold that dog studies conducted before large-scale human prevention trials are initiated can streamline the process of finding the most effective dose of cancer preventive, enabling oncologists to lob a well-aimed grenade at the cancer foe.

Pet dogs can assist in preventing human cancers in another way. For years dogs in the research lab have advanced understanding of the acute and long-term effects of high doses of cancer-causing chemicals. But pet dogs, just by going about their daily lives, could serve as sentinels—watchdogs, if you will—to identify substances in our homes and in our backyards that are carcinogenic at lower doses. If something can cause cancer, the disease will show up in pets, with their compressed life spans, well before it will in people.

Take asbestos. Most human cases of mesothelioma (a malignancy of tissues lining the chest and abdomen) stem from asbestos exposure. Symptoms can appear up to 30 years after the incriminating exposure. Investigators have now documented that mesothelioma in pet dogs is also largely related to encountering asbestos, most likely through being near a master who came into contact with it through a hobby or work. But in dogs, the time between exposure and diagnosis is comparatively brief—less than eight years. So the appearance of the cancer in a dog can alert people to look for and remove any remaining sources of asbestos. Also, closer monitoring of exposed individuals might lead to earlier diagnosis of mesothelioma and render these cancers curable.

WHY UNCLE BILL AVOIDED CANCER

BECAUSE CANCER in pet dogs is so commonplace, the animals might be able to assist in solving an age-old mystery. Almost everyone has an Uncle Bill who smoked two packs a day and never got lung cancer. So what factors determine cancer resistance? One way to tease out the answer is to find populations resistant to cancer and study them closely—their genetics, their diet and their lifestyle.

Such a population has been found—human centenarians. It turns out that most folks who live to be 100 die of disorders other than cancer. But it is nearly impossible to collect reliable information from a 102-year-old woman on her dietary habits and physical activity when she was a teenager or in her mid-40s. So Waters asked a simple question: Is this phenomenon of cancer resistance in the oldest old operational in pet dogs? The answer is yes [*see box at left*]. Now by interviewing owners of very old pet dogs, comparative oncologists can construct accurate lifetime histories of "centenarian" dogs. Combine this prospect with the

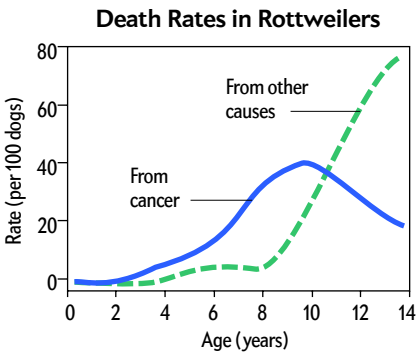
Cancer Resistance: Lessons from the Oldest Old

The risk of most human and canine cancers increases dramatically with age. This pattern has led to the belief that cancer is simply the result of a time-related accumulation of genetic damage. But studies of people who live to be 100 years old (centenarians) reveal an intriguing paradox: the oldest old among us are much less likely to succumb to cancer than are people who die in their 70s or 80s. Do the oldest-old pet dogs share a similar resistance to cancer mortality?

To answer this question, my colleagues and I consulted pet owners and veterinarians to construct lifetime medical histories of a large cohort of Rottweiler dogs living in North America. We found that the likelihood of dying from cancer within two years rose with age during adulthood until dogs reached about 10 years but then declined after that. Moreover, exceptionally old dogs (those older than 13 years) were much less likely to die of cancer than were dogs with usual longevity even though the risk of dying from other causes continued to rise.

These findings raise the exciting possibility that studies comparing oldest-old dogs to those with usual longevity might reveal genes that regulate cancer resistance. Gene variations (so-called polymorphisms) responsible for cancer resistance and exceptional longevity in dogs could then be evaluated to see whether they are also overrepresented in the oldest-old humans. If they are, scientists can try to learn how the molecular interactions regulated by these genes alter cancer susceptibility at the tissue level.

At present, the precise nature of cancer resistance in human centenarians is poorly defined. Detailed autopsy studies of oldest-old dogs are currently under way to explore this issue. These studies should determine whether cancer resistance reflects a complete suppression of the biological events that give rise to cancer—for example, through increased repair of DNA damage—or whether tumors actually arise but are of the nonlife-threatening variety. By better understanding the genetic and pathological basis of cancer resistance in the oldest old, scientists will be better positioned to develop practical interventions that will reduce a person's cancer risk. —*D.J.W.*



In Rottweilers that live past 10 years, getting older means having better odds of avoiding death from cancer.

GETTY IMAGES (*Rottweiler*)

ability to collect biological samples (such as blood for genetic analysis and for tests of organ function) from very old dogs as well as from several generations of their offspring, and you have a unique field laboratory for probing the genetic and environmental determinants of cancer resistance.

The puzzle of cancer resistance can also be addressed in another way—by examining differences in cancer susceptibility between dogs and humans. In people, obesity and diets rich in animal fat are known to increase risk for colon cancer. In contrast, colorectal cancer in dogs is uncommon, even though many pet dogs are obese and consume a high-fat diet. Scientists are now contemplating the use of dogs as a "negative model" of colon cancer in the hope of identifying factors able to confer cancer resistance to people whose style of living strongly favors colon cancer development.

A GROWING EFFORT

HISTORICALLY, comparative oncology research has been conducted in university-based hospitals and labs where veterinary oncologists are trained. But other organizations have begun to recognize the potential for this kind of research to translate into better care for people, and these institutions are now actively engaged in comparative oncology research.

The Gerald P. Murphy Cancer Foundation began in 2001 to accelerate the discovery of improved methods for preventing and treating prostate and bone cancers affecting both people and pets. To better understand the cancer-aging connection, the foundation's Center for Exceptional Longevity Studies has developed a database of more than 380 canine centenarians, focusing on uncovering the mechanisms of the cancer resistance that characterizes these longest-lived dogs. And in 2003 the National Cancer Institute developed the Comparative Oncology Program, which designs cancer treatment trials involving dogs with naturally occurring cancers.

The effort continues to grow. Since 2013 the Pfizer–Canine Comparative Oncology and Genomics Consortium Biospecimen Repository has provided the research community with clinical specimens collected from more than 2,000 pet dogs diagnosed with cancer. More recently, the NCI Comparative Brain Tumor Consortium was established so pet dogs with naturally occurring brain tumors could advance the rigorous pursuit of answers to critical questions related to human brain cancer that have not been adequately resolved either through rodent research or through human studies.

In other work, a longitudinal observational study of more than 3,000 pet dogs—the Golden Retriever Lifetime Study—has been launched to determine the genetic and environmental factors that impact cancer risk and other health outcomes. This decade-long cohort projectt, which enlists the assistance of veterinarians across the U.S., completed its enrollment in 2015. The need to obtain a richer understanding of the mutations within cancers, which could serve as targets for drugs, has given rise to several large-scale studies of human cancers. This same need is inspiring the Canine Cancer Genome Project. Launched by the Animal Cancer Foundation in December 2017, the canine project will map the mutational landscape of canine cancers and place these genomic data in the public domain with the intent of accelerating anticancer drug discovery that will benefit both pets and people.

Of course, there are limitations inherent in the use of animals to mimic human cancer—whether you are talking about rodents, dogs or other species. No single, ideal animal model for cancer exists [*see box on page 58*]. The best science is done by asking precise questions and then using the research tools most likely to yield meaningful answers. At times, following that rule in cancer research will mean turning to dogs to track down that hard-to-win knowledge.

The intriguing similarities between the cancers of people and pets—once a mere curiosity—are now being systematically applied to transform cancer from killer to survivable nuisance. Comparative oncologists are not inducing cancer in animals but are compassionately treating pet dogs suffering from the same kinds of lethal cancers that develop naturally in both man and man's best friend. They are putting our canine companions on the trail of a killer in ways that can save both pets and people. SA

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MORE TO EXPLORE

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