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Comparison of Cancer Incidence in Domesticated Versus Wild Animals, as the New Insight into the Cause and Prevention of Cancer in Humans

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***Abstract*—This review research article has gone through the cancer incidence in domesticated and wild animals. Cancer causes approximately 50 percent of deaths in pets over the age of 10. Some common types of cancers in pets include are skin, breast, head and neck, lymphoma, leukemia, testicular, abdominal, and bone. Cancers commonly found in pets that are also commonly found in humans are lymphoma, melanoma, and osteosarcoma. The two most common household pets, dogs tend to get cancer at a higher rate than cats. The cancer may be treatable depending on cancer type and the treatment options for dogs and cats are similar to those for humans. The cancer incidence in wild animals is much less than domesticated animals which are due to their lifestyle and nutrition type. The reason behind the cancer incidence in wild animals is the environmental parasites, viruses, bacteria and fungi. It seems the traditional lifestyle and nutrition is very important in the prevention of the cancer in humans as well.**

Keywords—Domesticated animals, wild animals, cancer, traditional nutrition

I. INTRODUCTION

Peto's paradox

Peto's Paradox is the observation, that at the species level, the incidence of cancer does not appear to correlate with the number of cells in an organism. [58] For instance, the incidence of cancer in humans is much higher than the incidence of cancer in whales. [59] This is despite the fact that a whale has many more cells than a human. If the probability of carcinogenesis were constant across cells, one would expect whales to have a higher incidence of cancer than humans. The same is true of elephants. In October 2015, two independent studies showed that elephants have 20 copies of a tumor suppressor gene TP53 in their genome, where humans and other mammals have only one, thus providing a possible solution to the paradox. [60]

P53 gene and the role in cancer

If the TP53 gene is damaged, tumor suppression is severely compromised. People who inherit only one functional copy of the TP53 gene will most likely develop tumors in early adulthood, a disorder known as Li-Fraumeni syndrome. The TP53 gene can also be modified by mutagens like chemicals, radiation, or viruses, increasing the likelihood for uncontrolled cell division. More than 50 percent of human tumors contain a mutation or deletion of the TP53 gene. [61] Loss of p53 creates genomic instability that most often results in an aneuploidy phenotype. [62] Increasing the amount of p53 may seem a solution for treatment of tumors or prevention of their spreading. This, however, is not a usable method of treatment, since it can cause premature aging. [63] Restoring endogenous normal p53 function holds some promise. Research has shown that this restoration can lead to regression of certain cancer cells without damaging other cells in the process. The ways by which tumor regression occurs depends mainly on the tumor type. For example, restoration of endogenous p53 function in lymphomas may induce apoptosis, while cell growth may be reduced to normal levels. Thus, pharmacological reactivation of p53 presents itself as a viable cancer treatment option. [64][65] The first commercial gene therapy, Gendicine, was approved in China in 2003 for the treatment of head and neck squamous cell carcinoma. It delivers a functional copy of the p53 gene using an engineered adenovirus. [66] Certain pathogens can also affect the p53 protein that the TP53 gene expresses. One such example, human papillomavirus (HPV), encodes a protein, E6, which binds to the p53 protein and inactivates it. This mechanism, in synergy with the inactivation of the cell cycle regulator pRb by the HPV protein E7, allows for repeated cell division manifested clinically as warts. Certain HPV types, in particular types 16 and 18, can also lead to progression from a benign wart to low or high-grade cervical dysplasia, which are reversible forms of precancerous lesions. Persistent infection of the cervix over the years can cause irreversible changes leading to carcinoma in situ and eventually

invasive cervical cancer. This results from the effects of HPV genes, particularly those encoding E6 and E7, which are the two viral oncoproteins that are preferentially retained and expressed in cervical cancers by integration of the viral DNA into the host genome. [67] The p53 protein is continually produced and degraded in cells of healthy people, resulting in damped oscillation. The degradation of the p53 protein is associated with binding of MDM2. In a negative feedback loop, MDM2 itself is induced by the p53 protein. Mutant p53 proteins often fail to induce MDM2, causing p53 to accumulate at very high levels. Moreover, the mutant p53 protein itself can inhibit normal p53 protein levels. In some cases, single missense mutations in p53 have been shown to disrupt p53 stability and function. [68] Suppression of p53 in human breast cancer cells is shown to lead to increased CXCR5 chemokine receptor gene expression and activated cell migration in response to chemokine CXCL13. [69] One study found that p53 and Myc proteins were the key to the survival of Chronic Myeloid Leukaemia (CML) cells. Targeting p53 and Myc proteins with drugs gave positive results on mice with CML. [70][71]

Materials and Methods

Cancer causes almost 50% of deaths in pets over the age of 10. Some common types of cancers in pets include: skin, breast, head and neck, lymphoma, leukemia, testicular, abdominal, and bone. Cancers commonly found in pets that are also commonly found in humans are lymphoma, melanoma, and osteosarcoma. [2] Of the two most common household pets, dogs tend to get cancer at a higher rate than cats. The cancer may be treatable depending on cancer type and the treatment options for dogs and cats are similar to those for humans. Surgery, radiation therapy, chemotherapy, and immunotherapy are all considered and will usually result in less side effects in animals than in humans. [3]

Cancer in Cats

Cats can get a variety of cancers. The most common are lymphoma, squamous cell carcinoma, mammary cancer, mast cell tumors, oral tumors, fibrosarcoma, osteosarcoma, respiratory carcinoma, intestinal adenocarcinoma, and pancreatic-liver adenocarcinoma. The disease has become so prevalent that it is now the most common cause of death in cats. [4] Certain breeds are more prone to certain cancers than others. Signs and symptoms are different depending on the type and stage of the cancer. Tumors that are visible or detectable by touch are most easily identified. The American Veterinary Medical Association recommends twice-a-year wellness exams for all cats. [5] Because the causes of cancer in cats are similar to those in humans, risk can be reduced by lowering the animal's exposure to harmful carcinogens, including tobacco smoke. [6]

Feline Leukemia

In humans, some viruses can lead to cancer. Papilloma virus or HPV, which is the causative agent of most cases of cervical cancer. Viral infection can also lead to cancer in animals. Feline leukemia (FeLV) is an RNA virus that infects less than 2% of healthy, domestic cats. [8] Infection is more prevalent in high-risk populations that mean cats with outdoor access or frequent social interactions. [7] The virus can spread from one cat to another via saliva, nasal secretions, feces, and milk. [9][10] It is transmitted during various forms of contact, from friendly grooming to biting. The virus can also be passed to a developing kitten during pregnancy. The age and time of infection affect the progression and clinical outcome of the virus. Kittens are more likely to be infected and more likely to develop more severe complications. [11] In most cases, FeLV initially infects lymphocytes in the oropharynx, which travel to the bone marrow, where virally infected cells are produced very rapidly. [12] In most environments, the Feline leukemia virus cannot survive for long outside of the host. It can be killed with soap and disinfectants. At this time, studies show no evidence that FeLV can be transmitted from infected cats to humans. [13] Infected animals may develop anemia or lymphoma. The FeLV-C subtype binds to and impedes the function of a heme transport protein on the surface of developing red blood cells. The result is a decrease in red blood cell numbers. [14][15] Signs of anemia in cats include paleness of the skin, tongue, gums, and mucous membranes surrounding the eye. FeLV- induced lymphomas are some of the most frequent tumors seen in cats. Symptoms depend on the location of the tumor, and may include weight loss, rough hair coat, loss of appetite, vomiting, diarrhea, respiratory distress, swelling of the lymph nodes and more. FeLV is also linked to diseases of the kidneys, joints, lymph nodes, small intestine, liver and nervous system. Depression of the immune system makes infected cats more susceptible to infections. Therefore, they may be infected by organisms that healthy cats usually fend off. It is possible for FeLV positive cats to remain healthy. However, the prognosis is poor for cats with persistent active infection. [12]

There are several different laboratory tests to detect FeLV. These include

1) an antigen enzyme-linked immunosorbent assay (ELISA)

2) an indirect immunofluorescent antibodyassay (IFA).

Both tests use blood samples to detect the presence of a protein that indicates FeLV infection. This protein is called p27, and is part of the structure of the virus. [12] Inconclusive results may require additional testing with other methods, such as a specific type of polymerase chain reaction (PCR), which can detect FeLV-DNA in infected animals. Infection with FeLV can be prevented by vaccination. The vaccine is classified as non-core, which means it

can be considered optional. However both the American Association of Feline Practitioners (AAFP) and the European Advisory Board on Cat Disease (ABCD) recommend that all cats with uncertain FeLV status and/or are at risk of exposure be vaccinated. Kittens are often vaccinated at 8-9 weeks of age and again at 12 weeks of age. Research shows that the vaccine will confer immunity for up to 1 year. Many vets recommend a booster vaccination 1 year after initial vaccination and annually thereafter. Because cats become less susceptible with age, some vets consider vaccination every 2-3 years sufficient for older animals. [12]

Feline Squamous Cell Carcinoma

Squamous Cell Carcinoma (SCC) is a cancer that occurs in cats and dogs. The tumors can appear many places but are seen most commonly on and around the eyes, ears, nose, mouth, and areas with little hair. The primary cause of SCC is sunlight over-exposure, which is especially harmful to fair-haired cats. Age and exposure to cigarette smoke also increase the risk for SCC. [16] At first, SCC tumors look much like other common skin irritations, making them difficult to identify. Scabs, hair loss, irritated skin, loss of teeth with limited healing, and raised red bumps on the skin are all possible sign of SCC. [16] Crusty sores can appear and develop into deep ulcers that bleed when irritated. In later stages, the cancer may spread to the lymph nodes and lungs. Staging of the cancer may involve chest X-rays and testing lymph fluid. [17] In advanced cases, SCC tumors can cause tissue death and destroy bone structure, leading to pain, discomfort, and possibly death.

Feline Mammary Cancer

Feline mammary cancer (FMC) is the third most common cancer in female cats. It is very uncommon in males, but some cases have been reported. [22] The mammary gland tumors that result from FMC can be benign or malignant. However, 80-96% of mammary tumors are malignant, meaning that they can invade nearby tissues, and are capable of metastasis. [22] Unfortunately malignant mammary tumors tend to be much more harmful. [23] Cats have four mammary glands on each side of their body, any of which can be affected by FMC. They are referred to as axillary, thoracic, abdominal, and inguinal glands. These glands are the sites of primary tumor growth. As with breast cancer in women, FMC is highly metastatic. As a result, this type of cancer can spread to the lungs, the lining of the lungs and pleura, liver, regional lymph nodes, and other parts of the body. Genes that have been targeted in human breast cancer research have also been studied in feline mammary cancer. HER-2/neu is the gene that encodes the human epidermal growth factor receptor protein. This protein resides on cell surfaces, where it can interact with growth signals. If gene amplificationcreates extra copies of the HER-2 gene, then its corresponding protein will also be overexpressed. This is thought to lead to increased cell proliferation. HER-2 overexpression has been detected in up to 30% of human breast cancer cases. [22] Similarly, it occurs in 30% of feline mammary cancer cases. [4] While all feline breeds may be affected by FMC, some are at a higher risk than others. [4] Studies have shown the Siamese breed to have twice the risk of developing this type of cancer. [22][24] Risk increases with age up to 14 years, with an average age of tumor development between 10 and 11 years. [23] According to one study, intact females are 7 times more likely to develop mammary tumors than cats that are spayed at a young age. [25] FMC is most often detected when pet owners or veterinarians feel a mass during examination of the mammary region. However, masses can also indicate other conditions, such as severely inflamed lesions, cysts, follicular tumors, and others. [4] Histology can be used to confirm the diagnosis and classify the lesion. Tumors are graded as well differentiated, moderately differentiated, or poorly differentiated, based on the appearance of the tissue-cells under a microscope. Tumor size is the most important prognostic factor in FMC cases, affecting the progression of the disease and the survival time. [4] Generally, larger tumors have a worse prognosis. Lymph node involvement and degree of metastasis also determine the severity of FMC cases.

Cancer in Dogs

Dogs have 35 times as much skin cancer as do humans, 4 times as many breast tumors, 8 times as much bone cancer, and twice as high an incidence of leukemia. [28] Other common types of cancer found in dogs include cancer of the mouth, lymphoma, testicular, and abdominal tumors. [2] Osteosarcoma, is most common in large dog breeds, such as Great Danes, mastiffs, Labrador Retrievers, and Rottweilers. [3]

Canine Transmissible Venereal Tumor

Cancer in humans is practically never transmitted from one person to another. Only very rare documented exceptions exist, usually involving surgical mishaps. Canine Transmissible Venereal Tumor (CTVT) is a very unusual form of cancer affecting canines. CTVT is transmitted by mating, licking, or other direct contact. [29] The tumor affects the genitalia. In some cases the urethra becomes blocked making it difficult for the affected animal to urinate. [30] If the cancer is located at the mouth and nose, nosebleeds, facial swelling, and nostril discharge are common symptoms.

Many human cancers are caused by viruses, including the human papilloma virus (HPV), a major cause of cervical cancer. Infection with viruses can lead to changes in normal cells within the infected person and lead to the development of cancer. However, CTVT is different. In this case, the cancer cells themselves are transmitted from animal to animal. Once in the new animal, the tumor can grow and eventually be spread to additional animals. [31] CTVT is not transmissible via killed tumor cells or by

cell contents. [29] Viruses are usually present in a cell's liquid contents. If the liquid contents do not transfer CTVT, it is evidence that viruses are not responsible for the cancer. Also, all tumor cells examined so far have a molecular fingerprint in their DNA that is absent in normal cells. Specially, the cancer cells contain a DNA sequence called Line-1 inserted near the oncogene c-myc. [32] Researchers have compared tumor DNA and normal DNA within different breeds of dogs. The results showed the expected differences between the normal cell DNA, but all tumor DNA samples were very similar despite being from very different dogs. These results indicate that the tumor cells themselves transfer CTVT between animals. [31] In most cases, the immune system recognizes and eliminates cells of other types that are introduced into an animal or humans. This does not happen with CTVT. Upon the initial infection, CTVT begins a state of rapid and intense growth that lasts anywhere from three to nine months and possibly longer in old or weakened dogs and This is usually followed by a variable regression phase. [29]

Canine Osteosarcoma

Osteosarcoma (OSA) is a cancer that develops within bones. It is often invasive and metastatic. [35] OSA is relatively rare in small domesticated animals, accounting for only 5-6% of canine malignancies. But, it is by far the most common primary bone tumor in dogs, accounting for 80% of cases. [36] This type of cancer occurs most commonly in the appendicular skeleton, including the radius and ulna, femur, tibia, scapila, humerus, and phalanges. The forelimbs are more likely to be affected than the hind limbs. OSA also occurs in the axial skeleton, including the spinal bones, skull, mandible, and the vertebrae at the base of the sacrum. In rare cases, it can affect extraskeletal tissues, such as muscle. [37] Because of its ability to metastasize, OSA can spread to other parts of the body and invades the lungs in approximately 17% of cases. [37] Osteosarcoma is more common in adult dogs. Large animals, weighing from 20 to 40 kg, are at a higher risk than smaller animals. [37] Large tumor size is associated with poor prognosis. [38] The location of the tumor can also affect the outcome of the disease. Axial skeletal OSA and appendicular OSA tend to have similar prognoses. [39] Tumors in the humerus bone tend to have a poor prognosis while tumors in the jaw tend to have better outcomes. [38][39]

Canine Hemangiosarcoma

Hemangiosarcoma (HSA) is a cancer that originates in cells that form blood vessels. HSA is responsible for approximately 7% of canine cancer cases. It is more common in dogs than any other species of animal examined. [44] HSA occurs most commonly in the spleen, skin, and the right atrium of the heart. [45] Primary tumors have also been reported in the lung, aorta, kidney, oral cavity, muscle, bone, urinary bladder, prostate gland, vagina, peritoneum, intestine, tongue, and conjunctiva. [46] HSA is highly metastatic. When HSA is confined to the skin, it is less apt to spread. Over 80% of all other cases have already metastasized at the time of diagnosis. [46] HSA cells may release proteins that stimulate the growth of new blood vessels. This process is known as angiogenesis, and is critical for tumor formation. The presence of numerous blood vessels helps supply growing tumors with nutrients and oxygen and may serve as a highway for the cancer cells to metastasize to distant parts of the body.

Older animals are at higher risk for developing hemangiosarcoma. Affected dogs are usually diagnosed between 9 and 12 years of age. [47] HSA tends to affect large breed animals more often than smaller ones. Breeds that are more prone to this type of cancer include German Shepherds, Golden Retrievers, Labrador Retrievers, Pointers, Boxers, English Settlers, Great Danes, Poodles, and Siberian Huskies. Breeds with short hair, light hair, light skin, or Whippets are more prone to hemangiosarcoma of the skin. [46][48][49] Symptoms of HSA vary depending on the location and stage of the cancer, but may include weakness, weight loss, tachycardia, tachypnea, abdominal swelling, lethargy, and paleness of mucous membranes. Episodes of acute weakness and collapse may indicate that a tumor has ruptured, causing uncontrolled blood loss. If internal bleeding occurs and the blood is reabsorbed from the body cavity back into blood vessels, the animal may gradually recover. In more severe cases, tumor rupture can cause sudden death. [46] Veterinarians often detect HSA during physical examinations. They also use blood tests, urine analysis, chest x-rays, abdominal ultrasound, echocardiogram, biopsy, and more. One type of blood test, the complete blood count (CBC), can detect anemia, misshapen or fragmented red blood cells, and other signs of HSA. Some tests can even indicate the organs being affected by the disease. A blood smear that shows normoblasts may indicate cancer of the spleen. [46]

Canine Mast Cell Tumors

Mast cell tumors, which also called mastocytomas, are the most common skin cancer in dogs. [51] Mastocytomas, develop most often in dogs seven and a half to nine years of age, but can occasionally be found in dogs as young as four to six months. Different breeds also have different rates of mast cell tumors. Boxers and Boston terriers have the highest rates. [52] Mast cell tumors originate from mast cells, immune system cells found in many tissues of the body. [53] Because mast cells can be found almost anywhere, mastocytomas have the potential to appear in all different regions of the body. They are most commonly located on the skin on hind legs, thorax, or genital regions. [54] Mast cells contain a variety of biologically active substances, including histamine, heparin, serotonin, and prostaglandins. These chemicals are released from the cells during an allergic reaction. [55] These are the substances that cause the symptoms associated with allergies.

Redness, itching, swelling, blood pressure drops, tearing, nausea and wheezing. Normally these chemicals are highly regulated, but when mast cells become cancerous, they no longer appropriately control the release of the chemicals. The unregulated release of chemicals by a mastocytoma can cause a variety of symptoms. The symptoms any particular dog shows is variable, but can include vomiting, ulcers, bloody excrement, abdominal pain, and blood-clotting difficulties; gastro-intestinal problems are the most common signs. [56] Mastocytomas appear as raised lumps that are often irritated or red in appearance. Mast cell tumors have no characteristic form or color and are impossible to identify without laboratory testing. [51] Often when a mastocytoma is touched the skin becomes red, itchy, and swollen. [52][57] This response is also called Darier's Sign. It occurs because when the mast cells in the tumor are compressed they release the chemical histamine, and this causes irritation of the skin. Although normal mast cells are typically fairly stationary, advanced mast cell tumors may metastasize to other places in the body. Veterinarians stage mast cell tumors using a six tiered system that is stages 0 to 5, based on the extent that the cancer has spread in the body. Staging takes into account the number and size of tumors, lymph node involvement, and recurrence rate. [51] A higher stage indicates greater body involvement with Stage 5 representing distant metastasis including bone marrow or blood involvement. [52] Another classification system, the histological grade which values from 1 to 3, is based on the physical appearance of the cells in the tumor. More abnormal mast cells-tissues are associated with a higher histological grade and have a higher possibility of being malignant. [52]

Cancer in Wild Animals

There are some types of cancers have been diagnosed in wild animals. Less is known about the cancers that affect wild animals, since they move around and may not be easily observed for a long period of time. Tasmanian Devils, Nowadays are plagued by an infectious cancer known as Tasmanian devil facial tumor disease (DFTD). Since the emergence of the disease in 1996, the population has declined by more than 60 percent. [72] George Washington University Medical Center researchers reported over thirty tumors found in elasmobranchs, a group of animals that includes sharks, rays, and skates. [73] In August of 2012, an article was published that described the discovery of melanoma affecting a population of wild fish. [74]

Cancer incidence in naked mole rats, due to the high amounts of hyaluronic acid, is rare. [75]

Although all analyzed human cancer genes are present in chimpanzee, cancer incidence in non-human primates is very rare. Additional factors contributing to the observed differences could include changes in diet, lifestyle or exposure to mutagenic agents, [76][77][78] physiological differences in immune system or in life expectancy and aging rates. [79]

The most interesting wild animal which can resist cancer incidence is elephant. A team led by Dr. Joshua Schiffman at the University of Utah set out to examine cancer rates in different species. They began by studying 14 years of autopsy data collected by the San Diego Zoo. They analyzed 36 species that spanned up to 6 orders of magnitude in size and life span ranging from the 51-gram striped grass mouse, which lives a maximum of 4.5 years, to the elephant, which can live up to 65 years. They also analyzed 644 documented deaths from a global database of captive African and Asian elephants. The researchers found no significant relationships between cancer risk and body size, life span, or basic metabolic rate among the species. For elephants, they estimated that the overall lifetime chance of dying from cancer was less than 5%. The lifetime cancer mortality rate for humans is about 20%. Elephants may have evolved to resist cancer by triggering apoptosis through p53 to efficiently remove mutant cells. [80][81][82]

Conclusion

Cancer incidence in the wolf is lower than that in the domestic dog. Cancer is low in the chimpanzee than in the human despite the two species having very similar cancer genes. The issue is not genetics, but it is the environment or gene-environmental interactions. Most chimpanzees eat their natural diet while in the wild or in captivity. It is likely that the incidence of cancer would be higher in chimpanzees that would eat a Western human diet. Germ line mutations might increase the incidence of some cancers, but only in a certain provocative environment. Cancer can occur in wild animals that are infected with certain viruses. Viruses can damage mitochondrial function thus producing cancer in the infected cells. The somatic mutations would arise as a downstream effect of the defective respiration. It is not clear if viral infections would be more common in domestic animals than in wild animals. Pollutants in the environment, including in the diet, would damage cellular respiration. Respiratory damage is largely responsible for cancer in both humans and domesticated animals that do not eat their natural foods.

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