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Using the canine genome to cure cancer and other diseases

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Abstract

A high-quality draft genome sequence of the domestic dog (*Canis familiaris*), together with a dense map of single nucleotide polymorphisms, has been reported. Such new tools offer scientists amazing opportunities to define genetic, nutritional, environmental, and other risk factors for various canine diseases. Because many of the diseases that affect man's best friend also affect us, understanding a dog's disease may lead to new preventions and therapies for diseases that affect both dogs and people. Since a dog's life span is shorter than that for a human, monitoring potential risk factors in a well-controlled population of dogs is possible. Such a population should be one where dogs live in close relationship with their owners. Although longitudinal studies have been previously conducted on animals housed in laboratory environments, the natural environment offers a chance to study dogs in environments shared by their owners. If dogs are carefully monitored, and select exposures defined, considerable information could be collected in a dog's lifetime—the next 10–20 years. Such information could hold the clues for important discoveries, including causes and cures for cancer.

Keywords: Cancer; Genome; Canine; Neoplasm; Neoplasia

1. Introduction

Numerous dog breeds have developed over the past two centuries and may represent one of the greatest genetic experiments ever conducted by humans [1]. As breeds differentiated from the tiny Chihuahua to the giant Great Dane, diseases also segregated amongst various breeds. In fact, many of the approximately 400 modern dog breeds show a prevalence of specific diseases, including cancers, blindness, heart disease, cataracts, epilepsy, orthopedic disease, deafness, diabetes, atopy, glycogen storage disease, neuropathies, reproductive disorders, and others [2,3]. The high prevalence of unique diseases within specific breeds suggests that a limited number of loci underlie each disease, making the genetic influence easier to identify in dogs than in humans [3,4]. In addition, because dogs have a shorter life span than humans and often have multiple siblings, it should be easier to identify not only genetic risk factors for disease and health, but environmental and nutritional components as well.

2. Cancer

One disease of tremendous significance for both dogs and people is cancer. In 2005, Morris Animal Foundation conducted an email survey of 2698 individuals who had donated money to advance animal health and welfare through the funding of research (Morris Animal Foundation, Donor Survey, 12 August 2005—unpublished data). Of those donors contacted, 696 (26%) responded to the survey. Over 70% of the respondents indicated that a dog was currently a member of their family household. The main health

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concern for donors with dogs was cancer, whereas the second health concern was heart disease (41 and 7% of respondents, respectively).

The National Cancer Institute estimates that there are over 4 million new cases of cancer diagnosed in pet dogs each year [5]. Although precise data is difficult to obtain in dogs since there is no mandatory ''death certificate,'' cancer is considered to be the leading cause of natural death in dogs [6]. In a study of over 2000 necropsy cases, 45% of dogs that lived to $\geq$10 years or older died of cancer [7]. With no age adjustment, 23% of the dogs presented for necropsy died of cancer [7]. Thus, dog owners have a reason to be concerned about cancer in their pets, and perhaps even more so than for themselves. Malignancies are reported to be twice as common in dogs as in humans [8].

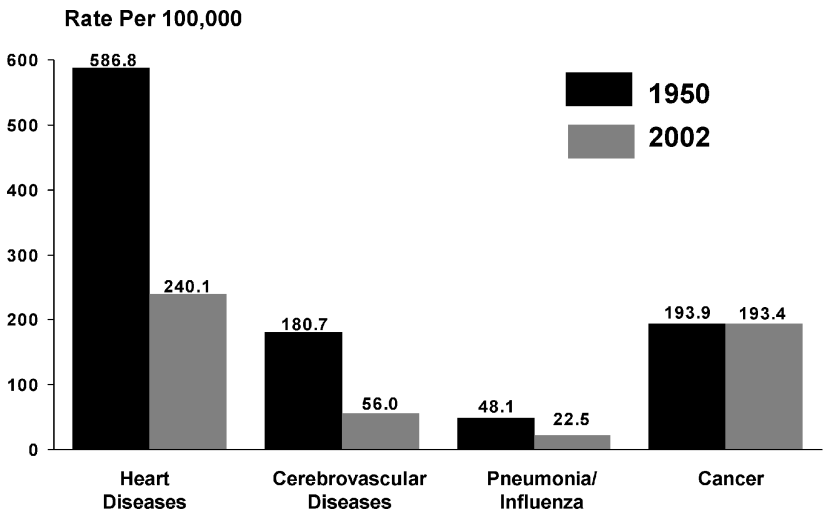
Although the National Cancer Act was passed in 1971, the war on cancer is far from won. More Americans will die of cancer in a 14-month time frame than have perished in all wars the nation has fought [9]. Although substantial achievements have been made for early detection and better therapies, cancer continues to be a leading cause of death. The change in the U.S. death rate from cancer, unlike some other major diseases, has remained stable since 1950 (Table 1).

Cancer has touched the lives of most people, either through the loss of a human or animal family member. Although the current statistics seem gloomy, the prospect for breakthroughs is very exciting and encouraging. Animal genomes have now been sequenced and offer a new approach for deconstructing disease. An emerging branch of science, called systems biology, is being developed which looks at genomes and the complex biochemical pathways created by the thousands of proteins that genes produce [10]. Leroy Hood, referred to as the godfather of this emerging branch of science, describes the genome as a list of parts, which when decoded is the key to curing disease. In 1981, Hood founded Applied Biosystems Group to commercialize his inventions; the company is still the leading provider of DNA analysis technology, with nearly $2 billion in annual sales [10]. An example of how new technologies will be used includes how individual animals or people metabolize drugs. Roche Pharmaceutical, in collaboration with Affymetrix – a firm that makes DNA chips – has produced a chip that can identify 31 genetic variations within two genes that affect how quickly individual people metabolize a variety of commonly prescribed drugs [11]. Whether prescribing common drugs, or drugs used to treat cancer, veterinarians and physicians will soon have new tools for selecting the most appropriate drug and the most appropriate dose for their patients.

3. Canine genome sequence

Sequencing of the canine genome offers exciting opportunities for cancer researchers. The unique breeding history of the domestic dog provides an

Table 1
Change in the U.S. death rates[a] by cause, 1950 and 2002 (human)



Sources: 1950 Mortality Data—CDC/NCHS, NVSS, Mortality Revised. 2002 Mortality Data: US Mortality Public Use Data Tape, 2002, NCHS, Centers for Disease Control and Prevention, 2004.

[a] Age-adjusted to 2000 US standard population.

unparalleled opportunity to explore the genetic basis of disease susceptibility, morphological variation, and behavioral traits [3]. Because dogs live in close proximity to humans, man's best friend also offers an unparalleled opportunity to address not only genetic risk factors for disease, but also nutritional and environmental triggers. Approximately 40% of all U.S. households include a dog, with the total number of dogs estimated at 73 million [12]. Dogs, living in close proximity to humans, are often afflicted with the same types of cancer than affect people [13]. Canine cancers also mimic those of humans in methods of metastasis.

4. Breed predispositions

There is no question that genetics plays a large role in certain breeds of dogs. The Broad Institute has identified breeds with increased risk (>4-fold) for genome-wide mapping studies. Examples include osteosarcoma (Greyhound), hemangiosarcoma (Golden Retriever), lymphoma (Golden Retriever, Boxer), melanoma (Scottish Terrier), mast cell (Pug, Golden Retriever), transitional cell carcinoma (Scottish Terrier) and others [personal communication, Dr. Kerstin Lindblad-Toh, 2006]. Other breeds at risk include Collies (nasal cancer), Rottweilers (osteosarcoma), Chows (stomach cancer), and Boxers (brain cancer) [13]. Because dogs have a shorter lifetime than humans, scientists should now be able to determine the genetic factors that cause one sibling to get cancer and another to be cancer-free. Thus, it is important to have genetic materials collected from both those dogs with cancer, and those dogs who have lived a long cancer-free life. Dogs older than 13 years are less likely to die of cancer [13]. A similar trend occurs in humans; those who live to be centenarians (100 years old) are less likely to die of cancer that those in their 70s or 80s [13].

5. Assessment of risk factors

Based on the odds ratio of a dog (within a specific breed) acquiring cancer, the number of dogs that need to be followed throughout their lifetimes can be predicted. Several organizations (e.g., Guide Dogs for the Blind, Inc., Guiding Eyes for the Blind, The Seeing Eye, greyhound associations) are already collecting and storing genetic samples in anticipation that researchers will soon be able to combine genotypic and phenotypic information to make predictions that will guide future breeding programs. Such studies will be important for predicting risk factors for cancer, but also for other genetically influenced diseases and temperaments. In addition to determining genetic factors, certain dog populations hold the potential to critically catalog a dog's environmental and nutritional risk factors. Research to answer critical questions about risk factors will require multiple partnerships: cancer researchers, epidemiologists, molecular biologists, pathologists, geneticists, veterinarians, dog owners and others.

6. Research funding

Concurrent with the great potential for new discoveries to advance animal health, the National Research Council has sounded the alarm that too few veterinary scientists are being trained in the USA [14]. In addition, the percentage of project grant applications receiving federal funding has been reduced in many areas [15]. Thus, private funders are receiving more requests to train scientists and to fund animal health studies. In 2005, Morris Animal Foundation received proposals from 481 scientific teams requesting over $36 million. The foundation was able to fund 55 new research projects and provide continued funding to 46 additional (multi-year) studies for a total of $4.3 million. Thus, the need to sponsor animal research is great and at a time when investments could reap significant new information on preventing and curing diseases.

In recognition of the need and potential for making rapid advancements, Morris Animal Foundation has launched an international effort to address both treatment and prevention of cancer in dogs. Since our foundation was established in 1948, we have funded over 100 traditional canine cancer studies. These studies have provided veterinarians with critical information and have also built a platform for scientific teams to now work together on novel therapies and prevention strategies. The Foundation now hopes to raise $30 million for this initiative, with all funding returned to the scientific teams that offer novel approaches for curing cancer in a dog's lifetime.

7. Conclusion

Our overall goal is to rid dogs of cancer. In our quest, dogs just might once again prove to be ''man's best friend'' and give us vital clues on how to prevent and cure cancer in ourselves.

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