Volume 4 • Issue 1 • 2020

Scientia Ricerca

Editorial Article

Medical Research and Clinical Case Reports

ISSN: 2578-3416

Cancer Incidence in Wild Animals and the Rejection of Peto's Paradox Theory

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Received: June 05, 2020; **Published:** June 09, 2020

Abstract

Cancer affects all animals containing eukaryote cells. 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. This review about cancers in wild animals contains useful data for the study of human cancers as well. Certain cancers in dinosaurs show that this metabolic disease is primitive and may have been around since the beginning of the multicellular organisms. This data also shows there has been some cancer types in naked mole rats and wild sharks as well. Nowadays, Tasmanian Devils 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. This type of cancer has an allograft transmission. It seems earthworms contain an anti-cancer agent which could be of great interests in the treatment of cancer. In the discussion part of our review we have discussed how Peto's Paradox theory of cancer is not true and we have mentioned many data of the cancer incidences in whales and elephants.

Keywords: *Cancer; Wild Animals; Eukaryote Cells; Multicellular Organisms*

Volume 4 Issue 1 June 2020

Abbreviations: DFTD: Devil Facial Tumor Disease; HPV: Human Papillomavirus; EMHC: Evolutionary Metabolic Hypothesis of Cancer; CT: Computed Tomography; CTVT: Canine Transmissible Venereal Tumor

Introduction

Cancer

Cancer is a group of diseases that involve abnormal cell division and growth, with the potential to invade or spread to other parts of the body which is called metastasis. [1] Not all tumors are cancerous. Benign tumors do not spread to other parts of the body. Possible symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. Although these symptoms may indicate cancer, they may have other causes. [2] Over 100 kinds of cancers affect mammalians. [3] Tobacco use is the cause of around 22 percent of cancer deaths. Another 10 percent is due to obesity, poor diets, lack of physical activity and drinking alcohol. [4] Other factors include certain infections, exposure to ionizing radiation and environmental pollutants and also certain viruses and parasites. [5] In the developing world, nearly 20% of cancers are due to infections like hepatitis B, hepatitis C and human papillomavirus (HPV). These factors act by changing the genes of a cell. Typically, many genetic changes are required before cancer develops. [6, 7] Based on S. Zaminpira and S. Niknamian Hypothesis, cancer is an evolutionary metabolic disease. [S. Zaminpira,

S. Niknamian, EC CANCER, ECRONICON, 2017]

Materials and Methods

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. [8] George Washington University Medical Center researchers reported over thirty tumors found in elasmobranchs, a group of animals that includes sharks, rays, and skates. [9] In August of 2012, an article was published that described the discovery of melanoma affecting a population of wild fish. [10] Cancer incidence in naked mole rats, due to the high amounts of hyaluronic acid, is rare. [11] Although all analyzed human cancer genes are present in chimpanzee, cancer incidence in nonhuman primates is very rare. Additional factors contributing to the observed differences could include changes in diet, lifestyle or exposure to mutagenic agents, [12-14] physiological differences in immune system or in life expectancy and aging rates. [15]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 [16-18].

Cancer in the First Living Eukaryote Cells

Based on Dr. Somayeh Zaminpira and Dr. Sorush Niknamian's Evolutionary Metabolic Hypothesis of Cancer (EMHC), cancer is not a disease and it has been occurred since the entrance of the mitochondrion into the first living cell as endosymbiont, and before the entrance of the mitochondrion all living cells had been using the fermentation respiration to produce its energy as ATP. [S. Zaminpira, S. Niknamian, Ecronicon, 2017]. Although it has been not found in fossils or observed in nature by scientists, we assume the first cancer cell is formed 1.5 billion years ago when the first living cells contained mitochondrion. The cause would be viruses or bacteria as parasites. [S. Zaminpira, S. Niknamian, LAP LAMBERT PUBLICATION, 2017].

Cancer in Dinosaurs

Cancer is a disease that has been around for millions of years. In a 2003 study, researchers used fluoroscopy and computed tomography (CT) to screen over 10,000 dinosaur vertebrae specimens for tumors. They found tumors in approximately 3% of the Cretaceous had Rosaurs specimens, but did not find tumors in any other dinosaur species. The tumors included hemangiomas, desmoplastic fibroma, and osteoblastoma. [19] In a research article conducted in 1999, metastatic cancer was found in only 1 out of 548 Edmontosaurus vertebrae sampled and was absent in all remaining samples. Hemangioma was present in 20 out of 669 Edmontosaurus vertebrae sampled and was absent in all 286 Corythosaurus vertebrae sampled as well as all 7,475 Sauropods, Ceratopsians, Stegosaurs, Theropoda, Ornithomimids, and Ankylosaurs vertebrae sampled. [20, 21] The statistically significant higher occurrence of hemangiomas found in hadrosaurs than in other dinosaur species suggests a genetic or environmental basis behind the pattern of tumor incidence. An example of an environmental factor could be the carcinogenic tannins, phenols, and resins found in the leaves consumed by these types of dinosaurs [21].

Tasmanian Devil Facial Tumor

Tasmanian Devils were driven to extinction on the Australian mainland thousands of years ago, after humans introduced dingoes to the continent. The remainder of the wild population has since inhabited the Australian island-state of Tasmania. In the mid 1990's the population reached an estimated 150,000 devils. [22] Nowadays, the animals 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. [23] This type of cancer is very unusual. The great majority of cancer cases in humans and animals arise from a series of mutations in a single precursor cell and its daughter cells. The process occurs over a period of years and does not involve contact with any other individuals. DFTD develops differently. It's transmitted from animal to animal and the cancer cells themselves are the infectious agent.

This phenomenon is called allograft transmission. An allograft is the term for the transfer of cells or tissue from one individual to another. An example in humans is organ transplantation. The movement of cancer cells between animals has been confirmed by cellular and molecular studies. A normal devil cell contains 14 chromosomes. [24] DFTD tumor cells contain several very distinctive genetic changes and have only 13 chromosomes. Importantly, the tumors from every animal tested appear identical. [24] Researchers in Tasmania also found a devil with an unusual chromosomal abnormality in its non-tumorous tissue that did not appear in its tumor cells. [24] These findings strongly suggest that the cancer did not arise from the animals' own cells. [25,26].

A cancer similar to DFTD occurs in dogs, and is known as Canine Transmissible Venereal Tumor (CTVT). The immune system of dogs is capable of overcoming the disease, but devils do not seem to be able to do so. Low genetic diversity among Tasmanian devils results in close kinship and reduces their immune responses. In conclusion, transplanted cancer cells are more likely to survive, grow, and spread. [27, 28] Transmission can occur by biting, feeding on the same material, aggressive mating, and other social interactions. DFTD tumors mostly form on the face and/or in the oral cavity. The cancer can also metastasize to other areas of the body. Nearly 100% of infected devils die within 6 months of the onset of clinical signs. [27] Death results from an inability to feed, secondary infection, or symptoms associated with metastases.

Cancer in Sharks

George Washington University Medical Center researchers reported over thirty tumors found in elasmobranchs, a group of animals that includes sharks, rays, and skates [29].

Cancer in Wild Fish

In August of 2012, an article was published that described the discovery of melanoma affecting a population of wild fish. Plectropomus leopardus which commonly called coral trout live along the Great Barrier Reef. Because the reef is located directly under the largest known ozone hole, it is thought that the cancer is due to increased exposure of the fish to ultraviolet (UV) radiation. Ozone normally absorbs the damaging UV rays, but ozone depletion allows the rays to reach the surface of the earth and the fish. No other causes of the cancer were identified in this study. UV light is the single greatest risk factor for the development of melanoma in humans [30].

Cancer in Sea Lions

During the 1960s and 1970s, persistent organic pollutants were dumped in California's coastal waters, where they bio-accumulated through the food chain. Twenty years later, people started noticing dead and stranded California sea lions. When examined, 20% of the sea lions were found to have cancer of the urinary and genital tracts and toxic chemicals in their blubber that had accumulated through the anchovies, squid, salmon and mussels they ate. [Cancer Registry for Companion Animals, Cornell University, 2013]

Cancer in Naked Mole Rats

Naked mole rats live up to thirty years which is a long life in this species. [31] Although cancer incidence increases with age, this disease was not observed in this species. By studying naked mole rats, researchers hoped to discover the keys to cancer resistance. Ironically, then, cases of cancer have been reported in naked mole rats. [32,33] These case reports indicate that naked mole rats are not resistant to cancer. One reason for this reported to be, hyaluronic acid, which was found to be much larger in naked mole rats than in other mammals [34].

Cancer in Earthworms

Earthworms have strong and very efficient cellular and humoral immune mechanisms adapting them to survive in their natural environment which is rich in pathogens. Numerous studies showed that earthworm proteins exhibit bacteriostatic, Cytolysis, antioxidant and anticancer properties. Cytotoxic components of Coelomic fluid including cytolysis factor or Coelomic cytolysis factor – eiseniapore, cause Lysis of vertebrate fibroblasts and erythrocytes. Moreover, proteins from Coelomic fluid may also increase expression of growth factors and assist in wound healing by stimulating proliferation and differentiation of fibroblasts and epithelial cells. In addition, the Coelomic fluid contains serine peptidases that means peptidase PI and PII, with very strong fibrinolytic and anticoagulant properties. Recently, numerous studies reported that earthworm proteins, in a concentration dependent manner, stimulate apoptosis of tumor cell lines in vitro and therefore are a potential source of anticancer agents [35].

The Coelomic fluid of earthworms exhibits different biological functions, including, bacteriostatic, proteolysis, cytolysis and mitogenic activities. In the present study, Coelomic fluid treated different cancer cell showed cytotoxic effect up to a concentration of 0.5 mg/ml. Coelomic fluid showed a dose dependent effect on above said cancer cells on detection with MTT assay. These results which show that HeLa cell inhibition at high concentration of Coelomic fluid were similar to those reported by Yan (2005) which stated that mass concentration of Coelomic fluid of earthworm Eisenia eugeniae, can kill HeLa cells by cell necrosis and lysis in a dose dependent manner. Kauschke and Mohrig, summarized that Eisenia eugeniae has a toxic effect on a variety of cell types, such as chicken fibroblasts. According to (Englemann *et al* 2003) the presence of cytotoxic molecules are released from a characteristic coelomocytes type from Eisenia eugeniae The Coelomic fluid of earthworms contains cytolysis and hem agglutinating molecules, which can be released from various Coelomocytes . Identication of different component proteins by HP-TLC technique was according to the method of Ueda., *et al*. (2004) the cytotoxic effect of Coelomic fluid of earthworms may be related to many components like proteins and peptides within the Coelomic fluid. Fibrinolytic activities, anti-tumor activities and microbial activities were found in Coelomic fluid by many researchers [36].

Discussion

Peto's Paradox

The challenge of suppressing somatic evolution that means cancer, dramatically increases with larger bodies and longer lifespans. If all mammalian cells were equally susceptible to oncogenic mutations and had identical tumor suppressor mechanisms, one would expect that the risk of cancer would be proportional to the body size and lifespan of a species. A greater number of cells in larger animals, and a greater number of lifetime cell divisions in long-lived animals, should increase the chance of accumulating oncogenic mutations. Some evidence exists that this is true within species [Altman and Schwartz 1978, Albanes 1998, Nunney 2013]; however, there is no indication that this relationship holds across species. It is well documented that carcinogenesis is an increasing function of age [Frank, 2007], and larger organisms generally have longer lifespans [Speakman 2005], which further suggests that we should see increased cancer incidence in large, long-lived animals. Peto's paradox is the clash between the theory that cancer incidence should increase with body size and lifespan, and the observation that it does not [Peto., *et al*. 1975, Peto 1977, Caulin and Maley 2011, Roche., *et al*. 2012].

On The Rejection of Peto's Paradox

A) Cancer Incidence in Zoo Animals

Necropsy data from animals in captivity confirms that cancer incidence does not increase with body size or lifespan across species varying orders of magnitude in both size and lifespan. We compiled 14 years of necropsy data collected by the San Diego Zoo (Griner 1983) and counted the recorded instances of tumors for mammals. In over 830 necropsies across 36 mammals we found a total of 37 incidences of cancer, which is only an overall incidence of 4.5%. A previous study, which did not require a minimum of 10 necropsies per species, found that 2.75% of species had neoplasms at the time of necropsy (Effron., *et al*. 1977). The highest rate of cancer in the data we analyzed was found in Tasmanian devils, though none of the cases were linked to the contagious facial cancer in that species.

B) Age and Lifetime Risk of Cancer in Elephants

Next we specifically investigated the cancer incidence in the largest extant terrestrial mammal, the elephant. If elephants had the

same biology as humans, and cancer incidence scaled linearly with the number of cells and lifespan of a species, with 100-fold more cells and lifespans up to 65 years (de Magalhães and Costa 2009), which is more than half the average human lifespan, elephants should get approximately 50-fold more cancers than humans. We analyzed data from the Elephant Encyclopedia (Koehl 1995 2012) on the cause of death for elephants in captivity in order to get an estimate of their age-incidence and overall lifetime risk of cancer. Out of 644 annotated deaths there were 20 cases of cancer/lethal tumors, resulting in a lifetime cancer incidence of 3.1%.

The true cancer incidence is obscured by the fact that necropsies are not performed on all of the animals at time of death and elephants are frequently euthanized for reasons such as arthritis, aggression and injury.

Many of the animals are euthanized because of "age related issues" which are unspecified and interfere with the cancer incidence data since this prevents many elephants in captivity from reaching the age at which they would naturally die. To get a more comprehensive estimate we calculated an inferred cancer incidence by assuming the same percentage of deaths with an unknown cause would be due to cancer as deaths with known causes. Using this calculation, the lifetime cancer death rate in elephants in captivity only increased to 4.8%, compared to the 25% lifetime cancer mortality rates in humans in the United States (ACS 2013) and 13% worldwide (Ferlay., *et al*. 2010).

C) Cancer in Whales

Whales are classified in the order Cetaceans, which contains two suborders, Odontoceti, the toothed whales including dolphins, and Mysticeti, the baleen whales including the humpback. Mysticeti and Odontoceti share a most recent common ancestor approximately 20-34 million years ago (Murphy, Pringle., *et al*. 2007, and Jackson., *et al*. 2009).

Humpback whales have an observed maximum lifespan of 95 years and have an average adult weight of 30,000Kg (de Magalhães and Costa 2009), though they can grow to as much as 48,000Kg (Schmidly 1994).

They are clearly a prime example of a large, long lived organism with which to study Peto's paradox. Very few cases of cancer have been reported in this species; however, there are documented cases of benign neoplasms including a basal lipoma in the central nervous system and fibromas on the tongue and skin (Newman and Smith 2006).

Humpback whales are closely related to species that are orders of magnitude smaller, such as the harbor porpoise (Phocoena pohocoena) (which we have plans to sequence with collaborators), which weighs approximately 52.5Kg (de Magalhães and Costa 2009). Close evolutionary relationships across magnitudes of body sizes make it more straightforward to determine genes involved with the evolution of large body size and long lifespan. Other research groups are beginning to sequence closely related cetaceans that span a range of sizes, which will enable many interesting comparative studies to be performed. The individual female humpback whale that was used for this sequencing project is already well known in the marine biology community and by local whale-watchers in New England. Her name is Salt and she was the first whale in the world to be assigned a name (as opposed to a number). She was first spotted by Captain Aaron Avellar in 1975 in Massachusetts Bay who named her for the distinct white scar pattern on her dorsal fin (Knaub 2001).

Salt has a history of helping researchers, as she was later seen that same year off the coast of the Dominican Republic which provided scientists with valuable information to understand the migration patterns of the North Atlantic humpback whales (NOAA 2006). She has been seen every year off the coast of Cape Cod for over 35 years, with the exception of one, and is estimated to be roughly 45 years old (Knaub 2012). Salt has mothered 12 calves and is a grandmother to 10 calves, all of which have been named by Captain Avellar and his family, whom continue to monitor Salt and her family from year to year (Knaub 2012).

The humpback whale population has been reduced from a global population of more than 200,000 to near extinction as a result of unregulated whaling (Clapham., *et al*. 1999). In recent years the population of humpbacks has been recovering and the current worldwide population is approximately 80,000, as reported by the International Whaling Commission (IWC 2013). Researchers have

used genetic markers to look at variation within the existing populations. They expected to see low diversity due to the extreme population ottleneck, however the populations maintain higher levels of nucleotide variation among individuals than expected, which is thought to be a preservation of the past heterogeneity as opposed to a recent post-bottleneck explosion (Baker., *et al*. 1993).

A full reference genome would allow for more in depth genetic studies for comparative biology as well as to better understand the current population and perhaps aid in continued conservation efforts. There are a number of other scientific communities that are eager for access to a baleen whale genome. The aging community would like to make use of this genome to gain insight into what genes may be responsible for the extended lifespans of whales. In order to transition successfully to marine life from their land-living ancestor, whales had to go through rapid adaptation and this evolutionary history remains encoded in their genomes, making this genome of great interest to evolutionary marine biologists seeking to understand this transition.

D) Cancer in Domesticated Versus Wild Animals

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. [S. Zaminpira, S. Niknamian, JMEST, 2017]

Conclusion

Almost all animals containing eukaryotic cells can get cancer. There have been some reports of cancer in Cretaceous hadrosaurs specimens, and this means cancer has been affecting dinosaurs as well. Tasmanian Devil Facial Tumor is an unusual cancer which is contagious and it is transmitted from animal to animal, and the cancer cells themselves are the infectious agent. There have been some reports of cancer in sharks and wild fish which shows this disease can affect submarine animals as well. The most eye catching cancer in wild animals is the type in naked mole rats which due to the high concentration of hyaluronic acid in their tissues and cell membranes, which can be of an important issue in human cancer treatment as well. For elephants, the estimation shows 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. Our study shows there is no relation between the age and the chance of getting cancer. It also shows there is no relation between the body size and cancer as observed in elephants, sharks, whales and humans. The point is, cancer in wild animals are rare in comparison with domesticated animals and humans. Peto's paradox has remained an unsolved mystery for more than 30 years (Peto 1977). There has been no observed correlation between body size, longevity and lifetime cancer risk. Every additional cell and extra year of life should increase the probability of carcinogenesis. The fact that large, long-lived organisms are not over burdened by cancer suggests that they are more resistant to malignant transformation than smaller, more short-lived animals. Since large, long-lived organisms have achieved cancer suppression with minimal toxicity, this may be a fruitful avenue for cancer prevention research. People have only been invested in cancer research for decades while evolution has been tuning cancer suppression mechanisms for over a billion years. If we can harness the cancer suppression mechanisms of large, long-lived organisms, then we could potentially eradicate cancer as a public health threat in humans.

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