The Mystery of Peto's Paradox

Jihyun (Olivia) Lim

Jihyun (Olivia) Lim [1]

Abstract

The mystery of Peto's paradox has perplexed evolutionary biologists for many years. The epidemiologist Richard Peto observed that while animals with larger bodies have more cells and therefore a higher likelihood of genetic mutation, they do not have a higher incidence of cancer. Identifying how larger animals have evolved to suppress cancer may help to resolve this apparent paradox. One hypothesis suggests that larger animals have evolved stronger cancer prevention systems, such as improved DNA repair mechanisms, increased sensitivity to apoptosis, or stronger defenses against uncontrolled cell division. Understanding how larger animals have evolved to resist cancer may help researchers identify new methods of cancer prevention and treatment in humans and animals. This review provides an overview of Peto's paradox and the development of cancer suppression mechanisms in large-bodied animals. We explore recent developments in understanding how larger animals have evolved to suppress cancer, including results from comparative and genomic studies. We also highlight new methods for fighting cancer that take advantage of the synergy between cancer prevention pathways.

Keywords

Peto's Paradox, metabolism, hallmarks of cancer, oncogenes, tumor-suppressor genes, apoptosis, somatic mutation, Klieber's Law, reactive oxygen species

[1] Corresponding author: Jihyun (Olivia) Lim, Chadwick International School, Yeonsu-gu Incheon, Republic of Korea. 22003, smilejlim2024@gmail.com

Introduction

Cancer results from uncontrollable cell division leading to disease in many organs. Cancer arises from genetic and epigenetic changes, often affecting pro-tumorigenic oncogenes and anti-tumorigenic tumor suppressor genes (1,2). The development and progression of cancer are characterized by a series of hallmark traits common to nearly all cancer types. These hallmarks include uncontrolled proliferation, evasion of growth suppressors, resistance to cell death, and angiogenesis (3,4). The purpose of this paper is to review the concept of Peto's Paradox, examine the molecular mechanisms by which oncogenes and tumor suppressors regulate proliferation, and explore the evidence for a link between cancer incidence and body size across different species (5). We will also explore the relationship between metabolism and cancer, emphasizing how metabolic adaptations or diet may help to explain Peto's paradox.

Background on Peto's Paradox

Peto's Paradox is an evolutionary conundrum that has long perplexed scientists and sparked a heated debate about the evolution of anticancer processes. The impact of natural selection on large body size, cancer susceptibility, and extended longevity is at the heart of Peto's Paradox. Investigating Peto's Paradox may thus significantly contribute to our understanding of anticancer mechanisms that could potentially be exploited for medical applications.

In 1977, Richard Peto discovered that a longer duration of exposure to the carcinogen benzopyrene was correlated to an increased likelihood of cancer progression. He later added body mass to the equation when he asked why humans have a relatively lower risk of cancer compared to mice despite having more cells and longer life spans. Furthermore, he noted that despite the higher theoretical hazards, cancer was not a prominent cause of mortality among many large and long-lived wild animals (5).

Many cells in a multicellular creature go through a cell cycle that includes division and growth. Every time a human cell divides, it must copy its six billion base pairs of DNA, and mistakes are unavoidable. These errors are known as somatic mutations. The difficulty of controlling somatic mutation increases in animals with larger bodies and longer lifespans. Cancer develops through the accumulation of mutations. Assuming that all proliferating cells have comparable likelihoods of acquiring mutations, each proliferating cell should be at an equal risk of malignant transformation. As a result, if an organism has more cells and more chances to form a tumor, the likelihood of developing cancer should rise. Similarly, if an organism lives for a longer period, its cells have more opportunities to collect mutations. Because the likelihood of carcinogenesis increases with age, an organism's lifetime risk of cancer should similarly increase with age. It is well understood that larger species have longer lifespans, which exacerbates the problem.

However, there appears to be no association between body size, longevity, and cancer among species— a conundrum that is referred to as Peto's Paradox (Figure 1). Peto's Paradox questions how natural selection has transformed the biology of huge, long-lived species to achieve this scaling. Cancer rates vary only about two-fold between multicellular animals, although the size variation between mammals can be on the order of a million-fold (5). Natural selection influences species' life histories and should reduce the risk of cancer during an organism's projected period of fertility. As a result, given an organism's age, it is expected that cancer rates would be similar across species. For instance, laboratory rats and humans differ in lifespan by a factor of 40 and size by three orders of magnitude. Nevertheless, around 30% of

both mice and humans are estimated to develop cancer (5). One possible explanation for Peto's Paradox is that giant, long-lived animals are more resistant to carcinogenesis than smaller, short-lived species; however, it remains unknown how larger species achieve this resistance (5).

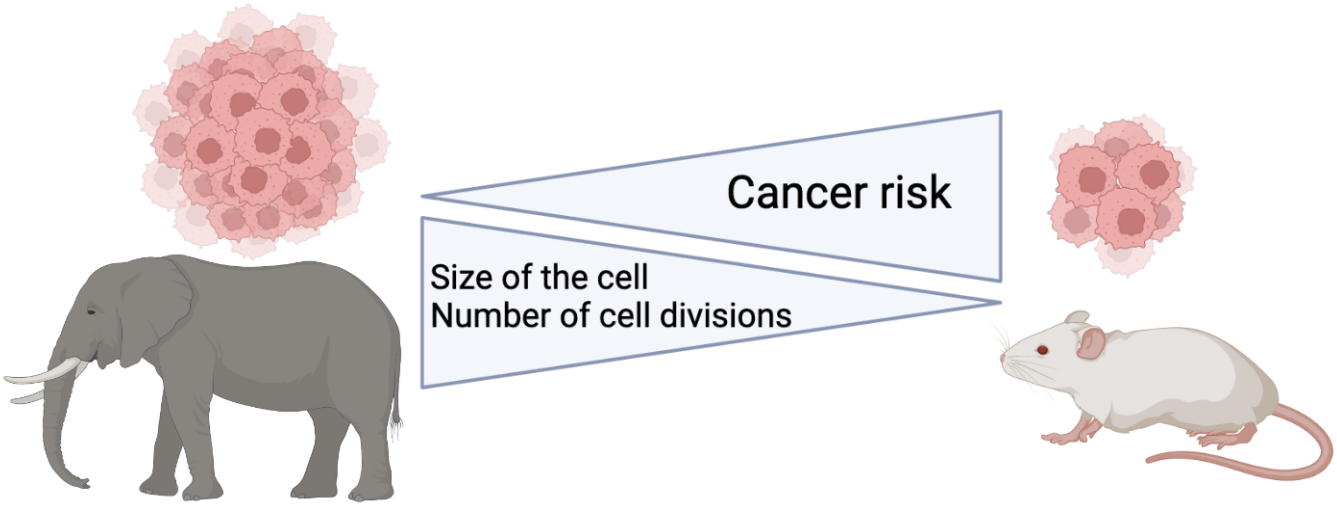

Figure 1. Two triangles represent the cancer risk and the number of cell divisions associated with animal size. The elephant is a large animal going through many cell divisions while a mouse undergoes relatively less number of divisions with a smaller cell size.

Oncogenic Mutations

Tumor suppressors help maintain homeostasis and act as safeguards against uncontrolled growth, which is one of the hallmarks of cancer. As critical defenders of genomic integrity and cellular regulation, tumor suppressor genes (TSG) exert tight control over cellular processes including cell cycle progression, DNA repair, and apoptosis (6,7). They act to limit tumor development and progression by monitoring and inhibiting uncontrolled cellular proliferation, underscoring their importance as regulators of cell proliferation and oncogenic potentials. Thus, tumor suppressors are commonly mutated in cancer, thereby allowing cancer cells to acquire the hallmarks of cancer. There are typically two copies of every tumor suppressor, and both of them must be lost or mutated to alter the function of the tumor suppressor (6,7). As somatic cells actively divide, they can experience mutations during DNA replication or as a result of exogenous damage. More cell divisions create a higher potential of mutations in the cells that lead to tumorigenesis. Some examples of important tumor suppressor genes are *TP53* (encoding p53) and *BRCA1* (BRCA1) (7). The impact of tumor suppressors to enhance cancer resistance could explain Peto's Paradox. An experiment to test the hypothesis might be to use genomic analysis to count the orthologs of known cancer genes in different species to quantify the copy number of cancer-associated genes. Functional investigations into the activity of tumor suppressors across species would complement sequencing information. Ultimately, understanding the complex processes governing tumor suppressor activity is critical for understanding the molecular foundation of oncogenesis and employing appropriate treatment approaches.

TP53 gene mutations have the greatest prevalence in human cancer. It encodes the p53 protein to regulate the cellular responses to DNA damage. p53 protein functions as a transcription factor to control gene expressions (6). The important cellular processes controlled by p53 target genes include cell division, DNA damage sensing, and repair, control of cell death, metabolism, and cell migration. Hence these p53 target genes help to suppress cancer by limiting the processes that promote the development of the hallmarks of cancer (7). Different mutations can impair the ability of p53 to suppress tumors. Among 50-60% of homozygous p53 gene mutations occurring in human cancers, about 90% of these mutations cause p53 to lose the ability to suppress cancer, or even gain new functions that promote cancer by encoding missense mutant proteins (7). When germline *TP53* mutations are inherited, they lead to a hereditary disorder known as Li Fraummeni Syndrome (LFS), a disease that increases a person's chances of acquiring cancer by 90% (6). Soft tissue and bone sarcomas, breast and brain cancer, adrenocortical tumors, and leukemia are among the most common cancers occurring in patients with LFS (6). LFS patients must be screened for cancer frequently beginning in infancy, given the high risk of childhood cancer that persists throughout their lifetimes. Currently, there are no medicines that target the p53 pathway (7).

BRCA1 is a gene that encodes another important tumor suppressor, the BRCA1 protein. BRCA1 aids in the repair of damaged DNA. Natural and medicinal radiation, chromosomal exchanges during cell division, and other environmental exposure can create DNA breaks (8). BRCA1 contributes to the stability of a cell's genetic information by assisting in DNA repair. Additionally, BRCA1 regulates the expression of other genes and plays an important function in embryonic development. BRCA1 interacts with several other proteins, including tumor suppressors and proteins that govern cell division, to suppress cancer (8).

Another crucial tumor suppressor gene is the retinoblastoma protein (Rb) which is often inactivated in cancer. Rb was the first tumor suppressor discovered and is recognized as a negative regulator of cell cycle progression (9). By controlling the activity of the E2F family of transcription factors, Rb regulates numerous cellular functions. While it plays a pivotal role in limiting cell cycle progression for its tumor suppressor function, research has revealed that many protein partners of Rb are engaged in other cellular processes that also contribute to tumor suppression (9). Many of the non-canonical roles attributed to Rb are linked to genomic instability, a cancer hallmark associated with poor prognosis, tumor heterogeneity, and the development of therapeutic resistance. The non-canonical activities of Rb include promoting DNA repair, chromosomal condensation and cohesion, centromere and telomere structure, and transposable element silencing are evident (9). The discovery of these non-canonical roles is essential as they aid in understanding how Rb inactivation leads to tumorigenesis and the development of therapeutics for retinoblastomas and other Rb-deficient tumors (9).

TSG redundancy may inhibit cancer in large animals by preventing cells from acquiring the mutations necessary to establish a malignant phenotype. Accordingly, human cells require more mutations than mouse cells to become immortalized in cell culture. To immortalize human fibroblasts, both the Rb and p53 pathways must be inactivated, but mouse cells only require the p53 pathway to be inactivated. Tumor resistance was increased in mice genetically altered to have additional copies of tumor suppressor genes such as *Trp53 or Cdkn2A*. Interestingly, the current elephant genome build (*Loxodonta africana*, Ensembl release 59) contains 12 orthologs of the human gene *TP53*, as well as one copy of each of the genes encoding the p53-family members p73 and p63. Each of these genes (*TP53, TP63, and TP73*) is found only once in the human genome (7). The increased number of copies of tumor suppressors may explain how

elephants may have such huge bodies and live such long lives (up to 70 years in the wild) while not succumbing to cancer at a higher frequency than smaller animals. Alternatively, larger animals might have fewer copies of proto-oncogenes (3). Having fewer proto-oncogenes would lower the likelihood of an oncogenic mutation occurring, and thus lower the overall risk of oncogenesis. Indeed research suggests that mice lacking the proto-oncogene *Hras1* grow fewer papillomas than wild-type mice (3). Genomes with fewer copies of proto-oncogenes would be less vulnerable to cancerous mutations that could generate the phenotypes required for cancer. Needless to say, proto-oncogenes have other tasks, so eliminating them could be harmful in other ways. Many tumor suppressor genes have a tissue-specific expression (6). Cells of larger species may have developed expression patterns in which more TSGs are expressed in any single cell than in smaller, shorter-lived animals, even if the genome contains the same number of TSGs (7). According to this concept, large animal genomes may contain more TSGs that are more widely expressed than smaller species.

The Hallmarks of Cancer and Their Role in Peto's Paradox

There are more than eight main hallmarks of cancer that grant cancer cells a selective growth advantage over healthy cells. Some of these hallmarks include angiogenesis, insensitivity to growth inhibition, resistance to apoptosis, invasion and migration, sustained proliferation, replicative immorality, changes in metabolism, and evasion of the immune system (3).

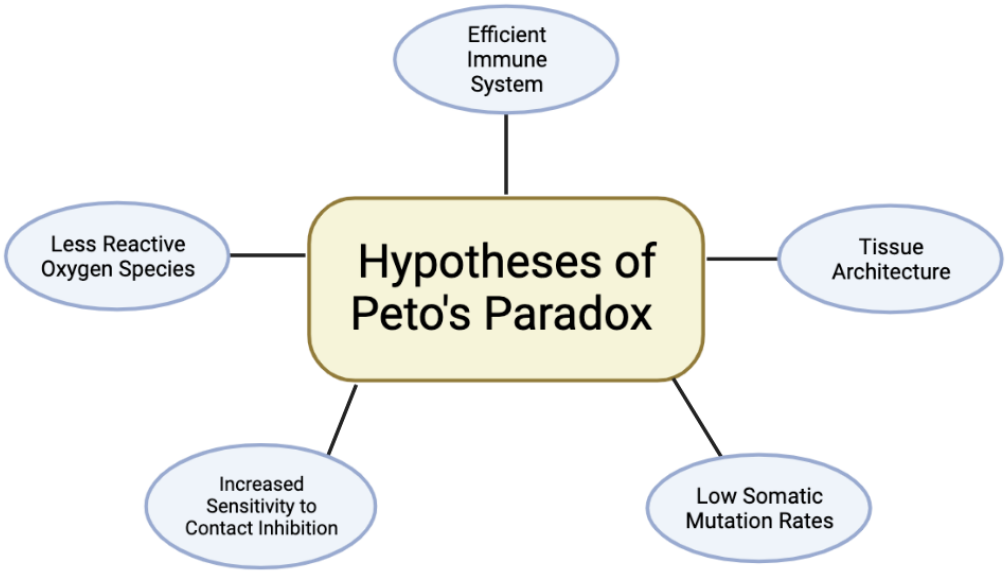

Figure 2. Five different hypotheses to support Peto's Paradox illustrated in circles

Evasion of the immune system is a critical hallmark of cancer. As tumor cells develop, they evolve mechanisms to avoid elimination by the immune system (10). Differences in immune surveillance may explain discrepancies in cancer resistance between species. In mice treated with carcinogens, the growth of tumors that are initially immunogenic is delayed due to enhanced immune system surveillance (11). However, as the tumor co-evolves with the immune system, unsuspected tumor variations are selected, giving rise to the phenomenon of immunoediting (12). Chronic antigenic stress may exhaust the immune system, resulting in poor surveillance, similar to what is observed in chronic viral infections. Large, long-lived creatures may have more effective immune monitoring for neoplastic cells than smaller organisms (12).

Cancer cells avoid the immune system in multiple ways including creating a microenvironment to compete for nutrients and suppress the immune system, signaling immune cells to stop attacking the normal immunosuppression mechanisms (12). Furthermore, when the tumor antigens are exposed for a longer time, cancer cells induce immune exhaustion by making the immune cells ineffective at attacking the tumor (3,12). To turn off the immune responses, immunosuppressive cells such as tumor-associated macrophages and regulatory T cells can be recruited (11). Hence it could be hypothesized that the mechanisms of immune evasion could be circumvented or decreased in larger animals. Larger animals such as the elephant may have a more active immune system that makes it harder to turn off or could have better mechanisms for recognizing the tumors (11). A follow-up investigation to test this hypothesis would be to assess the immunological response to cancer-associated proteins in different species.

Another hallmark of cancer that relates to Peto's Paradox is a change in tissue architecture that may affect the frequency of metastasis or the spread of tumor cells to new sites in the body. Metastasis is controlled by tissue architecture, cell compartmentalization, and cell motility dynamics (13). Many tissues, such as the crypts of the intestines, are made up of tiny proliferative units containing multipotent stem cells and progenitor cells (11). The hierarchical structure of tissues from undifferentiated stem cells to differentiated daughter cells has been postulated as an important aspect of cancer development (13). As differentiating cells are evolutionary dead-ends, the effective population size of a somatic tissue is likely to be determined mostly by the number and dynamics of stem cells. However, a mutation that interrupts differentiation in a non-stem cell may also result in a cancerous cell lineage by causing dedifferentiation of the cell into a more 'stemlike' state (11,13). By simply adding non-stem phases to a "serial differentiation" model, it is possible to increase the number of cells and the rate of cell turnover without increasing the number or proliferative activity of somatic stem cells (12,13). Changing the number of stem cells, crypt density, or differentiation and division dynamics could improve the tissue's ability to resist malignant transformation.

Signals from the microenvironment can also decrease 'selfish' cellular proliferation (11). Cell contact inhibition, for example, differs between human, mouse, and naked mole-rat (*Heterocephalus glaber*) cells. Due to the early activation of the p16 pathway, which leads to hypersensitivity to contact inhibition, naked mole-rat cells cease dividing at considerably lower densities in culture than human and mouse cells (3,11). Although naked mole rats and mice are both small species, naked mole rats live substantially longer (28 years) than mice (4 years). Cancer was not found in any of the 250 necropsies performed on dead naked mole rats in captivity (2,10). Although only observed in vitro, hypersensitivity to contact inhibition may have developed to suppress cancer and allow the naked mole rat to live longer (10). Similarly, early

cell senescence signals could be activated in huge, long-lived organisms to stop unchecked growth.

If larger animals have lower somatic mutation rates per cell generation, more cell divisions would be required for a cell to acquire the essential mutations to become malignant (12). The mutation rate is determined by the error rate of DNA replication and the rate at which errors are fixed (2,12). This could be accomplished via a variety of strategies, including improved DNA damage detection and repair systems. Experimental findings, on the other hand, show that mice and humans have comparable mutation rates (11,13). However, the hypothesis that larger animals have lower somatic mutation rates could be tested by measuring and quantifying somatic mutation in vivo in different species.

Cells' susceptibility to programmed cell death, known as apoptosis, may differ between large and small creatures. Cells from huge bodies may be more vulnerable to DNA damage or the activation of oncogenes, making them more prone to apoptosis (14). Observations of human and mouse cell cultures lend support to this notion. When human cells are irradiated, many die as a result of apoptosis caused by DNA damage. Despite the extensive DNA damage caused by the radiation, a higher percentage of mouse cells survive and continue to divide (14). Apoptosis caused by DNA damage removes the injured cell from the population rather than fixing the DNA and potentially propagating residual mutations in the tissue (11,14). However, there is likely to be a trade-off between apoptosis preventing cancer and generating senescence as a side effect.

Changes in Metabolism

Metabolism is present when foods are converted into energy and raw materials with the help of cells for growth or repair. The ultimate purpose of metabolism is ATP production which releases the primary energy source used for cell division and growth (12). Not only entailing a breakdown of macromolecules of catabolism, but metabolism also plays a crucial role in the development and progression of cancer. As cancer cells go through metabolic changes, they adapt to the unique challenges of the tumor microenvironment (15).

Cancer cells undergo profound metabolic changes, allowing them to adapt to the unique challenges of the tumor microenvironment. The shift toward aerobic glycolysis, known as the Warburg Effect, is one of the most well-characterized changes (12, 15). The Warburg Effect occurs when cells preferentially use the anaerobic glycolysis pathway to produce energy from glucose, even in the presence of oxygen, rather than the more efficient oxidative phosphorylation process. This metabolic shift allows cancer cells to produce more of the building blocks required for cell growth and division (15). Alterations in lipid, amino acid, and nucleotide metabolism are among the many metabolic changes commonly observed in cancer cells (10, 15). These changes may allow cancer cells to adapt to the limited nutrients and oxygen often found in the tumor microenvironment, allowing them to survive and proliferate despite hostile conditions. The link between metabolism and cancer is intricate and multifaceted (15). While metabolic changes can help cancer cells survive and grow, they can also make cancer cells vulnerable to metabolic inhibition. This has resulted in the development of a new class of cancer therapeutics that target cancer cells' metabolic vulnerabilities.

If reactive oxygen species can cause carcinogenesis, then the pace of metabolism may correlate with the rate of cancer in animals of various sizes (18). A comprehensive assessment of marine mammal cancers referenced studies with very large numbers of necropsies, and the findings indicate that whales had considerably lower cancer rates than smaller mammals like the

sea lion (19). An examination of a global database of over 15,000 wild or captured elephants tends to confirm Peto's Paradox. Of the 616 dead elephants in the experiment, 18 (approximately 3%) have been linked to cancer; however, these figures do not offer a lifetime cancer rate (19). Nonetheless, these results suggest that elephants do not frequently die from cancer, compared to 12.5% of human deaths from all types of cancer. (18). Natural mouse fatalities with aging have been reported for over 2000 mice, with approximately half succumbing to cancer by 800 days of age (18). These data appear to corroborate but do not prove Peto's Paradox's broad contention.

Klieber's Law

One explanation for Peto's Paradox relates to differences in metabolic rate between species. The relationship between animal body mass and the amount of heat production per day has been recognized for many decades, beginning with the observations of Max Klieber in the 1930s. Klieber discovered that body mass correlates with ¾ the power of the whole body basal metabolic rate (B= M $\frac{3}{4}$; where M is body mass) (16). The exact magnitude of Klieber's law, such as $\frac{2}{3}$versus $\frac{3}{4}$, has been a source of contention. The basal metabolic rate is related to heat loss through body surface area, which is more directly related to the $\frac{2}{3}$ power (16). A updated review of existing data reveals that the power function is closer to $\frac{3}{4}$ than $\frac{2}{3}$, while there is significant variations across mammalian subgroups (11,16). It is worth noting that the mass-specific metabolic rate B' is defined as B/M and reflects metabolic rates normalized to tissue mass, such that B' = M$\frac{1}{4}$: the slope equals the exponent when plotted as logB' versus logM (17). From a biological standpoint, this power function is visible in mice's substantially greater metabolic rates, which implies orders of magnitude higher than that of elephants. These differences in metabolic rate could account for Peto's Paradox.

West, Brown, and Enquist (WBE) proposed a theoretical explanation for the $\frac{3}{4}$ power law function, focusing on nutrition supply through the geometry of the circulatory system (16, 17). In essence, a theoretical model of the circulatory system was studied that resembled a fractal network branching down to the end capillaries. If the branching pattern is replicated from the aorta to the capillaries, the end capillary density in this model would predict the rate of nutrient perfusion to cells, which controls the metabolic rate. According to this hypothesis, the larger the animal, the sparser the capillary density in tissues (17). The increased inter-capillary distance is considered to result in lower nutrition delivery and a steeper oxygen gradient from blood vessels, resulting in decreased respiration and oxidative phosphorylation and, ultimately, decreased specific metabolic rates (17).

Nagy et al. offered a different idea of Peto's conundrum regarding the formation of hyper tumors. Within a natural selection, tumors may favor cheater cells that use vasculature created by angiogenic cells. These cheaters have the potential to expand and parasitize the original tumor. The hyper-tumor would lower the tumor's overall fitness and may even lead it to retreat (11). According to Nagy et al, deadly tumors must be significantly bigger in larger animals, providing the hyper tumor more time to grow and forcing the parent tumor to necrotize (11, 21). This model predicts that big animals would frequently carry macroscopic tumors that will be proportionally more necrotic than tumors in smaller creatures (21). As a result, increased necrosis in the larger tumors of large-bodied animals could limit tumor growth and reduce the

likelihood of cancer mortality (11, 21). However, the hypothesis is not empirically proven in laboratory conditions. Additionally, it is difficult to experimentally compare the fitness of different cell populations in a tumor, making this model difficult to test.

Reactive oxygen species (ROS) are produced by redox reactions involving the movement of electrons. ROS are generated in two ways: from endogenous sources inside the body, such as oxidative mitochondrial metabolism; and from exogenous sources arising from external factors such as ultraviolet radiation. Intracellular ROS impact cellular damage, oncogenic transformation, genome instability, hyperproliferation, immortalization, angiogenesis, and more (18). While moderate ROS levels are required for normal cellular functions, an increased metabolic rate or mutations in certain cancer-associated genes may elevate the ROS production in tumor cells (18, 19). Hence relatively higher metabolic rates in small animals compared to their body mass would lead to more production of ROS from the mitochondria (19). This might consequently result in more mutations in DNA and thus a higher likelihood of cancer risk, which supports Peto's Paradox.

However, in 2021, a study collected a large dataset from 'Species360' and 'Zoological Information Management System' which is an international non-profit organization to test Peto's Paradox computationally. These collected zoo animals involve a variety of species under human supervision with regrouped information from 1,200 zoos worldwide. When examining living organisms within distinct taxonomical classifications such as primates, carnivores, Rodentia, artiodactyls, and Chiroptera, it becomes evident that carnivores exhibit a relatively higher risk of cancer development (20). This observation suggests that the consumption of meat and the dietary habits of carnivores entail a heightened susceptibility to oncogene activation (20). One plausible explanation supporting this hypothesis is that a diet rich in fats and low in fiber represents a significant contributing factor to cancer incidence among carnivores (20). Moreover, carnivores predominantly occupy the highest trophic level, thus implying increased exposure to bioaccumulated carcinogenic compounds, including pollutants (20). Notably, the consumption of raw meats by carnivores further intensifies their exposure to pathogens, which exacerbates the oncogenic transformation (20). Consequently, the increased mortality risk resulting from cancer incidence primarily affects carnivores, specifically due to their unique metabolic characteristics.

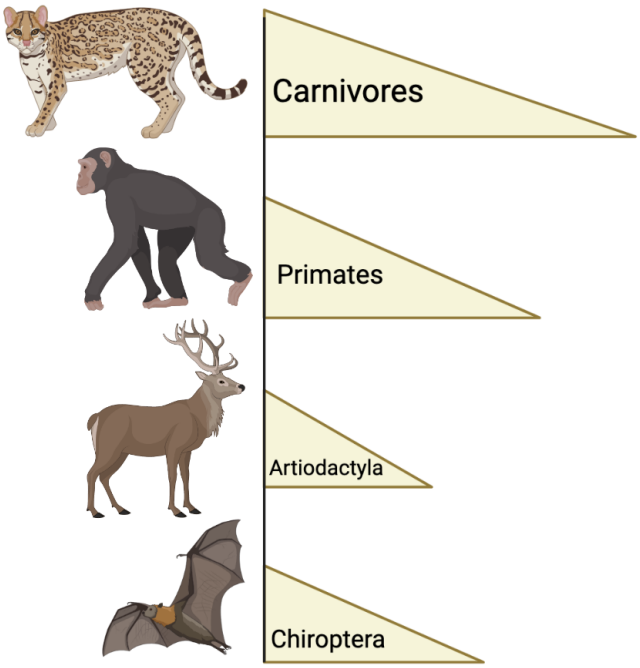

Figure 3. Different sizes of triangles show the comparative degree of cancer mortality risk associated with various taxonomy of species

Conclusion

This review paper discussed the hypotheses that underpin Peto's Paradox as it relates to the comparative relationships among different species of animals like the mouse and an elephant. Presently, there exists limited data to substantiate this hypothesis. However, a database study investigating the correlation between a carnivorous diet and cancer risk provides empirical evidence that supports this paradox. Peto's Paradox is an important mechanism to gain a comprehensive understanding of the fundamental hallmarks of all types of cancer. Although Peto's Paradox primarily focuses on the multispecies of animals, a better understanding will lead to valuable insights into human cancer. Consequently, a refined understanding of cancer will facilitate enhanced cancer treatments for humans.

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Authors

Jihyun Lim, the author of this article, is a rising 12th grade at the Chadwick International School, Incheon, South Korea. Her passion for life sciences and biology field has motivated her to write this review paper about Peto’s Paradox with the help of Amy Tarangelo.