A Reexamination of Peto's Paradox: Insights Gained from Human Adaptation to Varied Levels of Ionizing and Non-ionizing Radiation

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ABSTRACT

Humans have generally evolved some adaptations to protect against UV and different levels of background ionizing radiation. Similarly, elephants and whales have evolved adaptations to protect against cancer, such as multiple copies of the tumor suppressor gene p53, due to their large size and long lifespan. The difference in cancer protection strategies between humans and elephants/whales depends on genetics, lifestyle, environmental exposures, and evolutionary pressures. In this paper, we discuss how the differences in evolutionary adaptations between humans and elephants could explain why elephants have evolved a protective mechanism against cancer, whereas humans have not. Humans living in regions with high levels of background radiation, e.g. in Ramsar, Iran where exposure rates exceed those on the surface of Mars, seem to have developed some kind of protection against the ionizing radiation. However, humans in general have not developed cancer-fighting adaptations, so they instead rely on medical technologies and interventions. The difference in cancer protection strategies between humans and elephants/whales depends on genetics, lifestyle, environmental exposures, and evolutionary pressures. In this paper, we discuss how the differences in evolutionary adaptations between humans and elephants could explain why elephants have evolved a protective mechanism against cancer, whereas humans have not. Studying elephant adaptations may provide insights into new cancer prevention and treatment strategies for humans, but further research is required to fully understand the evolutionary disparities.

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Keywords

Carcinogenesis; Radiation; Biological Evolution; Radiobiology; Peto's Paradox, Evolution

Introduction

Peto's paradox is a phenomenon in epidemiology that was first identified by the British epidemiologist, Sir Richard Peto, in the 1970s [1]. The paradox refers to the observation that, despite the fact that larger animals have more cells and are thus more likely to develop cancer, they do not have a higher incidence of cancer compared to smaller animals. Peto's paradox has been observed across a range of species, including humans, and has led researchers to explore the role of evolution in cancer development, as well as the potential for identifying new strategies for cancer prevention and treatment [2]. Since then, there have been numerous studies exploring and attempting to explain the paradox, and

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it remains an active area of research in cancer biology and epidemiology.

Adaptation to a living environment is a process as old as life itself on Earth. This phenomenon occurs when there are significant changes in the environment or when a species is introduced to a new environment, such as the potential colonization of humans on Mars [3]. It's important to note that evolution does not always result in the best possible adaptation to a particular challenge [4]. Evolution is a process of trial and error, and adaptations that are successful in one context may not be in another [5]. Moreover, evolution works within the constraints of existing genetic variation, and there may not always be sufficient variation available to produce the optimal adaptation to a particular challenge [6]. Adaptation happens when a species has enough time to develop new abilities that allow it to survive in the new environment. Genetic variation within a species can also lead to adaptation, where some individuals are better able to adapt than their counterparts due to competition [4].

An accumulating body of evidence shows that humans have been adapted to their environment through evolutionary processes. There are numerous examples of adaptations of humans to their environment including:

1. High-altitude adaptation: People who live at high altitudes have evolved to have larger lung capacity and a greater capacity for oxygen transport in their blood. This adaptation allows them to thrive in areas with low oxygen levels, such as in the Andes Mountains or the Himalayas [7].

2. Resistance to disease: Humans have also evolved to be resistant to certain diseases. For example, people who are descended from populations that have historically lived in areas with high rates of malaria have developed a genetic trait that provides resistance to the disease [8].

3. Sweat glands: Humans have more sweat glands than most other animals, which allows them to regulate their body temperature more efficiently. This adaptation has been crucial to the survival of humans in hot environments [9].

4. Lactose tolerance: Another example of human adaptation is lactose tolerance. People who come from cultures that have a long history of dairy farming have evolved to be able to digest lactose, the sugar found in milk. This adaptation is thought to have emerged as a way to ensure a steady source of nutrition, particularly in areas where food was scarce [10].

Human Adaptation to Ionizing and Non-Ionizing Radiations

In this Perspective, we discuss human adaptation to different levels of both ionizing and non-ionizing radiations, including Ultraviolet (UV) radiation and ionizing radiation. While these forms of radiation can have harmful effects on human health, humans, like many other species, have evolved various mechanisms to protect themselves from their harmful effects.

A. Adaptation to Ultraviolet Radiation

Throughout the history of life on Earth, UV radiation has been present in the environment. Humans have developed various mechanisms to protect themselves from the harmful effects of UV radiation. One such mechanism is the production of melanin pigments, which can absorb UV radiation and prevent damage to the DNA in skin cells [11]. People living in areas with high levels of UV radiation, such as near the equator, have darker skin pigmentation to protect against skin damage and skin cancer. Conversely, people living in areas with low levels of UV radiation, such as near the poles, have lighter skin pigmentation to allow for better absorption of sunlight and the synthesis of vitamin D [11].

B. Adaptation to Ionizing Radiation

Certain locations, like Kerala, India, and Ramsar, Iran, stand out for their elevated natural radiation levels. This phenomenon is attributed to the presence of radioactive materials within their soil and water sources [12, 13]. Interestingly, research suggests that inhabitants of these regions may have developed adaptations over generations, allowing them to better tolerate this increased radiation

exposure [14]. A study conducted in Kerala provides a prime example. It revealed that individuals residing in areas with high radiation possessed more efficient cellular DNA repair mechanisms compared to those living in areas with lower radiation levels [14].

Humans are inherently equipped with mechanisms to combat the harmful effects of various radiation types, both ionizing and non-ionizing. These adaptations enhance our ability to withstand radiation exposure, particularly in regions with naturally high background radiation. A highly influential scientific paper (cited over 500 times on Google Scholar) has provided valuable insights into the biological effects experienced in such high background radiation zones [13]. This study specifically explored the biological consequences of exposure to exceptionally high levels of natural background radiation in Ramsar, Iran. Despite receiving radiation doses exceeding 260 millisieverts (mSv) per year, significantly higher than permissible levels for radiation workers, residents in these high background radiation areas did not exhibit considerably higher rates of chromosomal abnormalities or other health problems compared to those in areas with normal background radiation [13]. The study instead suggests that long-term exposure to natural background radiation might trigger a cellular response that safeguards against radiation-induced damage.

Furthermore, Ramsar holds the distinction of having some of the world's highest natural background radiation levels, with certain areas exceeding those found on the Martian surface [15]. This phenomenon arises from the presence of radium-rich hot springs in the region. These springs lead to the accumulation of radioactive materials (radionuclides) in the local environment (soil, water, and air), consequently increasing radiation levels [15]. However, it's important to note that radiation levels on Mars are generally lower than those in most natural background radiation areas on Earth. The average radiation dose on the Martian surface is approximately 0.67 millisieverts per day [16]. A crucial distinction exists between the types of radiation on Mars and Earth. Mars's thin atmosphere allows cosmic rays (high-energy particles from space) to penetrate the surface more readily compared to Earth's thicker atmosphere [16].

While humans have evolved adaptations to protect themselves from ultraviolet (UV) or ionizing radiation, it's essential to understand that these adaptations don't offer complete protection from skin cancer [11]. In contrast with humans, elephants have developed a unique strategy to safeguard themselves from cancer, and this strategy appears to be linked to their unique genetic makeup [11].

The Roots of the Difference

The key question is how the evolutionary differences between humans and elephants account for elephants' protective mechanism against cancer. While it's not entirely accurate to say that elephants and whales don't get cancer, their incidence of cancer is much lower than that of humans and other smaller animals [12, 13]. This may be due to several factors: fewer cell divisions, more efficient DNA repair mechanisms, increased cancer suppression mechanisms, and adaptations to reduce cancer risk [12, 14].

However, the reasons for the lower incidence of cancer in larger animals are still being studied and understood. Elephants and humans have different life expectancies, reproductive strategies, and rates of aging, which can influence the evolution of cancer resistance strategies.

Recent research has shown that elephants have multiple copies of a tumor-suppressor gene called TP53, which plays a crucial role in preventing the development of cancer [15, 16]. Elephants also have additional copies of other cancer-fighting genes, such as LIF6, which can induce programmed cell death in damaged cells. These extra copies of cancer-fighting genes appear to have evolved through natural selection, likely due to the fact that elephants have long lifespans and a low rate of reproduction, meaning that cancer would have

a significant impact on their fitness [17].

Elephants possess 20 copies of suppressor genes in their genome, whereas humans have only 1. These genes are responsible for DNA checks, and when they detect a mutation, the cell either undergoes apoptosis or repairs it. The TP53 gene produces a protein that stimulates apoptosis, which is crucial for preventing cancer. Recent research has shown that when exposed to DNA damage, elephant cells initiate apoptosis more frequently than human cells [18, 19].

Humans, on the other hand, have evolved different strategies to ensure reproductive success, such as having many offspring over a shorter lifespan. In addition, many cancers in humans are thought to be caused by environmental factors, such as exposure to carcinogens or lifestyle factors like smoking or poor diet, rather than solely by genetic factors [20]. While humans do have some tumor-suppressor genes like TP53, they may not have evolved as many copies as elephants due to different evolutionary pressures [15].

Additionally, the passage of time is a significant factor in evolution and adaptation. Elephants have been around for 10 million years [21], while human's origin date back to 5-8 million years ago [22]. Therefore, elephants have had more time for positive mutations to occur. It is possible that in a few million years, humans may also develop similar mutations that help suppress cancer.

In Figure 1, height data and cancer rates are obtained from the World Population Review website and the World Cancer Research Fund International website, respectively. Both refer to male populations in Europe to reflect homogeneous living standards and geography. As shown in the Figure 1, although European heights are similar (with a maximum difference of 9.41 cm), cancer rates vary across the continent. This may be due to differences in suppressor genes, which can lead to lower rates of cancer in some nations. For example, as indicated in Table 1, the Finnish population has an average height of 180.57 cm and a cancer rate of 277.6 per 100,000 men, while the Slovenians have an average height of 180.9 cm and a cancer rate of 354.3 per 100,000 men. It is possible that, just as people in Ramsar have adapted to radiation, the population in Finland has adapted to more cells.

Conclusion

Humans have evolved mechanism to somewhat protect themselves from UV or ionizing radiation because these types of radiation are a common threat in the environments that humans have inhabited throughout their evolutionary history. Therefore, it is not surprising that humans have evolved adaptations such as melanin pigmentation which help to protect against the harmful effects of UV radiation and the ability to produce vitamin D in response to UV exposure.

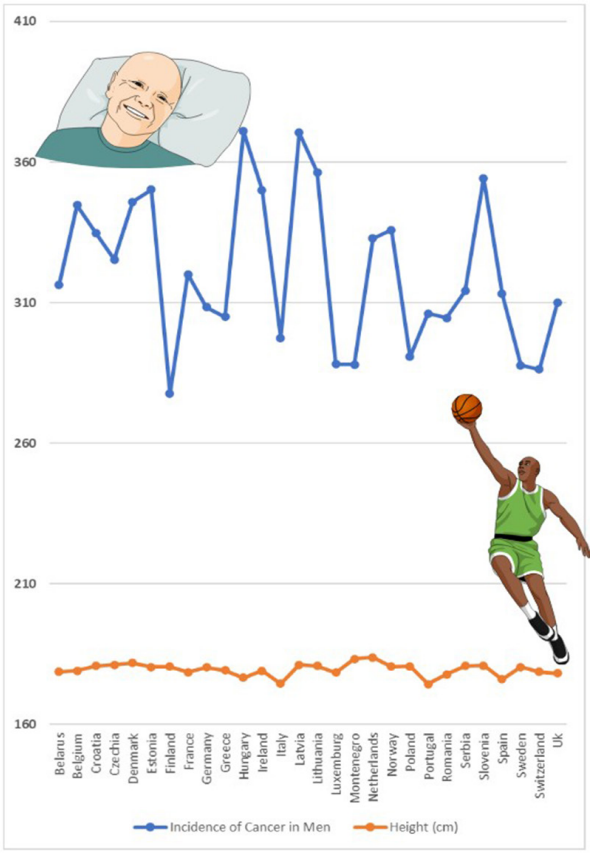

Figure 1: Variations of cancer incidence in men and their average height in European countries.

Table 1: Incidence of cancer in men and the average male height in some European countries.

Country	Incidence of Cancer in Men	Height (cm)
Belarus	316.4	178.69
Belgium	344.7	179.09
Croatia	334.8	180.76
Czechia	325.4	181.19
Denmark	345.9	181.89
Estonia	350.2	180.34
Finland	277.6	180.57
France	320.1	178.60
Germany	308.4	180.28
Greece	305.0	179.26
Hungary	371.0	176.59
Ireland	350.1	179.04
Italy	297.5	174.42
Latvia	370.4	181.17
Lithuania	356.4	180.72
Luxemburg	288.1	178.43
Montenegro	288.0	183.30
Netherlands	332.8	183.78
Norway	335.9	180.48
Poland	290.7	180.69
Portugal	306.1	174.37
Romania	304.5	177.82
Serbia	314.2	180.74
Slovenia	354.3	180.98
Spain	313.1	176.11
Sweden	287.7	180.40
Switzerland	286.3	178.73
Uk	309.9	178.21

In contrast, elephants and whales have evolved adaptations to protect themselves from cancer, such as a high number of copies of the tumor suppressor gene p53. These adaptations are thought to be related to their large body size and long lifespans, which increase their risk of developing cancer. However, it is important to note that humans do not have multiple copies of the p53 gene and other tumor suppressor genes, which play a critical role in preventing cancer.

The difference in cancer protection strategies between humans and elephants/whales is not entirely related to genetic makeup alone. While genetics certainly play a role, other factors such as lifestyle, environmental exposures, and evolutionary pressures also influence the development of cancer protection strategies. For example, humans have developed medical technologies and interventions that can help prevent or treat cancer, which may have reduced the evolutionary pressure to develop additional cancer protection strategies.

Taking these factors into account, elephants have developed a distinctive array of genetic adaptations that help to prevent cancer. This is likely due to some key factors. The combination of their large size, extended lifespan, low reproductive rate, and unique genetic adaptations has made elephants highly resistant to cancer. Studying these adaptations may provide insights into new cancer prevention and treatment strategies for humans. Humans have not evolved the same protective mechanisms, owing to their dissimilar life histories and exposure to different environmental factors. To fully understand the evolutionary disparities between humans and elephants with regards to cancer prevention, further research is required to address key questions in this field.

Authors' Contribution

SMJ. Mortazavi, SAR. Mortazavi and L. Sihver conceived of the presented idea. These authors also developed the theory and performed the preliminary studies. All authors have contributed to the gathering of data and the writing/reviewing of the current manuscript and read, modified, and approved the final version of the manuscript.

Conflict of Interest

SMJ. Mortazavi and L. Sihver, as the Editorial Board Members, were not involved in the peer-review and decision-making processes for this manuscript.

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