A biological paradox offers new insights into the mystery of cancer

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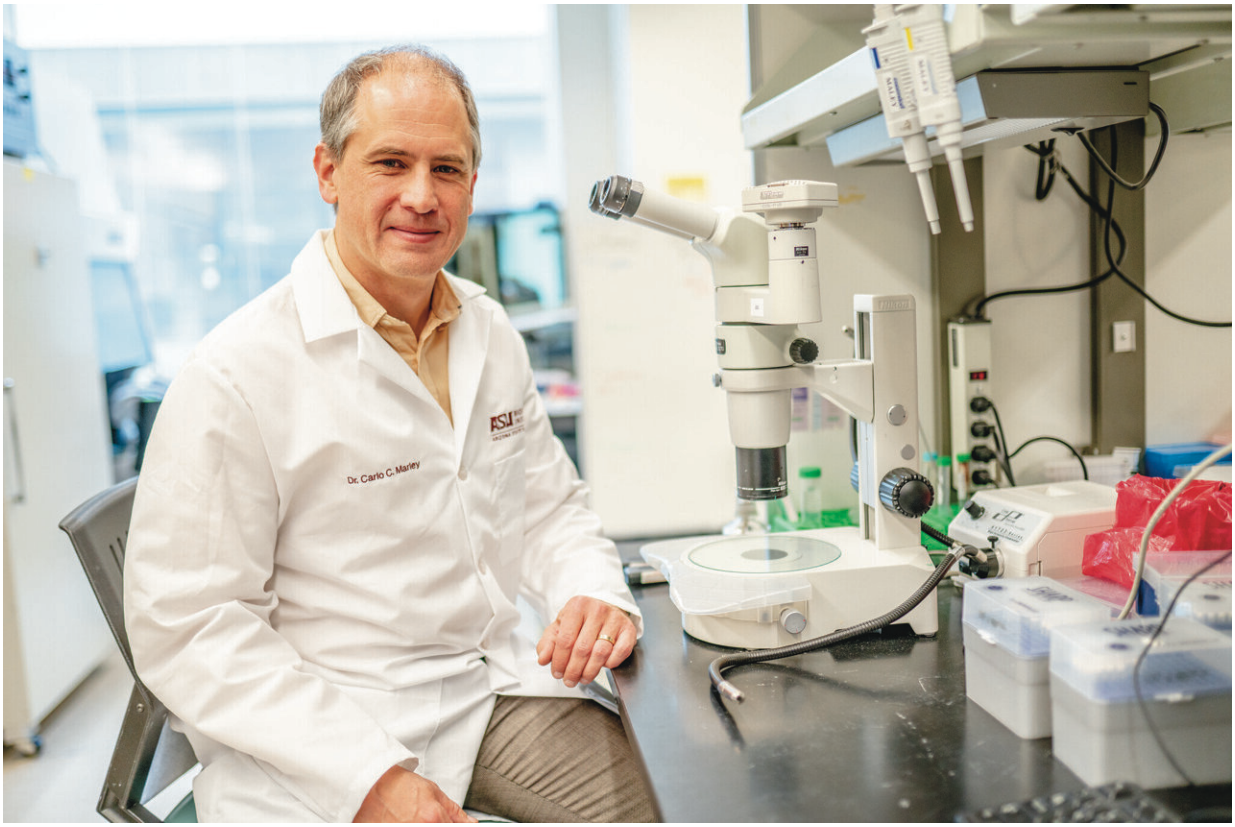

Carlo Maley is a researcher with the Biodesign Center for Biocomputing, Security and Society at Arizona State University.Maley is also researcher with the Biodesign Center for Immunotherapy, Vaccines and Virotherapy and the Biodesign Center for Mechanisms of Evolution at Arizona State University.He's an associate professor at ASU's School of Life Sciences and director of the Arizona Cancer Evolution Center. Credit: The Biodesign Institute at Arizona State University

The cells in the body can be thought of as tiny archery targets, each vulnerable to the deadly arrow of cancer. The more cells a given animal has and the longer it lives, the greater its odds of accumulating harmful cell mutations that can eventually lead to cancer. Or at least, this is what intuition suggests.

Nevertheless, many very large animals bearing huge cell populations, including elephants and whales, not only survive to old age, but have remarkably low rates of cancer. This biological enigma bears the name Peto's paradox. In short, the paradox says that species size and longevity should be proportional to cancer incidence, yet the real-world data across species suggest this association does not hold.

In a new study appearing in the journal *Nature*, Carlo Maley, a researcher with the Biodesign Center for Biocomputing, Security and Society at Arizona State University, along with international colleagues, explore recent implications of Peto's paradox and highlight what science is learning about cancer across the tree of life.

The researchers analyze the largest cross-species database of its kind—a pool of adult mammalian life from zoo records that includes 110,148 individuals spanning 191 species.

The aim is to assess species-specific cancer mortality rates across a wide assortment of mammals, re-examine the claims of Peto's paradox in a rigorously quantitative way and explore possible cancer-suppression mechanisms relevant for fighting the disease in both humans and animals.

The study provides the most intensive evaluation of Peto's paradox to date. The findings offer conclusive proof that cancer mortality risk is largely independent of both body mass and adult life expectancy across species.

The solution to the paradox lies in the fact that the evolution of greater size and longevity in species has been accompanied by the co-evolution of potent mechanisms of cancer resistance.

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Ceaseless battle

The fight against cancer has logged some recent victories. Annual statistics for 2020 reveal the largest single-year drop in cancer mortality ever recorded, according to the American Cancer Society. Yet despite significant advances in the diagnosis and treatment of cancer, the disease remains a leading killer, with an estimated toll of over 600,000 last year in the U.S. alone.

The scourge is not limited to humans. Indeed, the new study reports a significant cancer burden across species, particularly among some mammals under human care, where the death toll from cancer in the adult population can reach an astonishing 20-40%.

While cancer is a fact of life across the entire range of multicellular species on earth, the disease is hardly democratic in selecting its victims. Some species have significantly higher or lower cancer rates, for reasons that researchers are still working to puzzle out.

The new study explores some of the surprises, including unusually high cancer vulnerability of some carnivorous mammals. The disparity was found to be closely associated with diet, with the highest cancer rates found in mammals that consume other mammals, though other factors

also play important roles.

More cells, more problems?

Multicellular organisms, from simple to highly complex, face challenges when their cells divide. Cell mutations can arise when DNA copying mechanisms fail to faithfully duplicate the 6 billion base pairs of the genetic code. Environmental factors such as radiation can also damage DNA integrity, leading to mutations.

Most such mutations have no perceptible effect on an organism's health. Some, however, trigger a devastating chain reaction, resulting in cancer, an often-lethal affliction.

The problem can be exacerbated when organisms grow large, acquiring more cells in their bodies. Another key factor is the accumulation of mutations over time, with age representing a key risk factor for cancer. The trend is readily observed in a variety of species, including dogs and humans.

But while this commonsense rule applies within a given species, researchers see something quite different when looking across a broad range of diverse species, where large, long-lived species are often seen to flourish with low rates of cancer.

This apparent contradiction was first expressed by epidemiologist Richard Peto. He studied cancer rates in humans and mice, finding cancer incidence in the two species approximately equivalent. Given that humans have roughly 1000 times more cells than mice and live 30 times longer, this presents a conundrum. Even more surprising is the observation that large and long-lived wild animals do not appear to show markedly greater propensity for cancer.

It appears that nature has confronted the problem of cancer in large, long-lived species and arrived at a number of solutions, which differ according to the species involved. These cancer suppression mechanisms may offer clues for suppressing cancer in other animals, including humans.

Probing a paradox

Although the fundamental insights of Peto's paradox have long been recognized, scientific confirmation has been challenging. Until now, the available data have been insufficient in terms of sample size, age-distribution, species relatedness and cause of mortality to draw firm conclusions in support of Peto's paradox.

The current study takes advantage of a large data set known as the Zoological Information Management System (ZIMS), which compiles detailed information on age, sex, dead/alive status and postmortem pathological data for adult non-domesticated mammals. This rich storehouse of cross-species information was crucial for a thorough analysis of Peto's paradox.

High cancer risk was observed in the zoo survey among carnivores. This may be due to the use of progestins and other forms of hormonal contraception as well as postponement of pregnancy in zoo animals. Both factors have been linked with the development of human cancers, as well as in non-domestic cats.

Yet the researchers determined that contraceptive practices cannot fully account for the heightened cancer risk among carnivores. If they could, a clear sex-bias in the data would be evident, with female carnivores showing higher cancer rates. Rather, a key determinant appears to be diet.

Diet as destiny?

Carnivores typically consume a high fat, low fiber diet, which is a known risk factor for cancer. Because carnivores are at the top of the food chain, they can ingest pollutants or other carcinogenic compounds at more concentrated levels that animals that appear lower on the food chain.

Further, the consumption of meat can expose carnivores to various pathogens that have been linked with processes of cancer formation. Viruses in particular can present considerable cancer risk, with 10-20% of all cancers believed to have a viral origin.

Further analysis of the zoo data showed that among carnivores, those that consumed other vertebrates as a regular part of their diet had the highest rates of cancer, compared with carnivores that rarely or never consume other mammals. The data suggest a high cost in terms of cancer risk for a carnivorous diet, particularly one rich in mammalian prey.

Other factors that could affect cancer rates in these animals include low microbiome diversity, the degree of physical exercise in captivity, or other physiological factors. In contrast to the carnivores, ruminants were found to have the lowest cancer risk among mammals.

Talking to the animals

The study results confirm the central assumptions of Peto's paradox. The data show no significant association between cancer mortality risk and body mass across species, suggesting that natural selection of cancer resistance mechanisms in large animals are what markedly reduce their risk of carcinogenesis.

These varied mechanisms have already become the focus of intensive research for their potential to prevent this deadly disease, both in wild animals and in humans, though much remains unknown. The study provides the basis for further explorations in this area and highlights the power of zoological data for future cancer research.

More information: Orsolya Vincze, Cancer risk across mammals, *Nature* (2021). DOI: 10.1038/s41586-021-04224-5. www.nature.com/articles/s41586-021-04224-5

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