frontiers | Frontiers in Ecology and Evolution

TYPE Hypothesis and Theory
PUBLISHED 26 February 2025
DOI 10.3389/fevo.2025.1489294

OPEN ACCESS

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RECEIVED 31 August 2024
ACCEPTED 12 February 2025
PUBLISHED 26 February 2025

CITATION
Uzoigwe CE (2025) Peto's paradox: 2 problems 2 answers.
Front. Ecol. Evol. 13:1489294.
doi: 10.3389/fevo.2025.1489294

Peto's paradox: 2 problems 2 answers

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Peto's paradox throws down the gauntlet to researchers to explain why larger animals have the same cancer risk as more diminutive species, notwithstanding the much higher cellularity of the former. Any explanation of the paradox must also contend with the fact that larger animals have a greater longevity and thus longer for their greater number of cells to undergo mutagenesis. The Paradox comprises two questions. The first is why larger animals exhibit the same tumor risk as smaller animals. The second is why those with greater longevity do not have a higher cancer risk than more ephemeral species. The Paradox has appeared so elusive as it has been often assumed that any single explanation must account for both phenomena simultaneously. In reality Peto's paradox comprises two problems with two distinct solutions.

KEYWORDS

Peto's paradox, immunosurveillance, immunoediting, cancer, mutation rate, ageing, body mass

Introduction

The concept is intuitive. Cancer is a stochastic process. It is thought to be the result of mutations triggering immortality with dysregulated growth and replication. On this basis species with a greater number of cells should have higher risk of cancer due to a greater pool of cells that could potentially undergo mutagenesis. However there is no correlation, across species, with regard to body mass and cancer risk. This is the infamous and apparently irrefragable Peto's paradox. It remains a pervasive finding. A number of distinct methodologies and paradigms have consistently reaffirmed the veracity of the paradox (Dart, 2022; Gorelick and Naxerova, 2022; Mammals and mutations, life span, cancer risk, 2022; Vincze et al., 2022).

Intuitively the paradox can only be accounted for by decreased carcinogenesis or increased elimination of neoplastic cells. Within this broad dichotomy a number of explicatory hypotheses have been proffered to account for the paradox. Nunney crystalized these in to 5 models.

Reduced mutation rate

1. Intrinsic changes in metabolic rate with body size: Cellular replication is the substrate of carcinogenesis. If cells do not divide at all or divide very infrequently the risk of cancer is significantly mitigates.

2. Decreased somatic mutation rate: This relates to the fidelity of DNA replication. Mutations and oncogenic proteins can occur to due to errors in translation and transcription. If no mutations or mutant effectors arise during these processes, due to an increased accuracy of replicative or transcriptive events, cancer is less likely to develop.
3. Increased genetic control via tumor suppressor genes or otherwise: Certain tumor suppressor genes if mutated or functioning aberrantly allow dysregulated cellular replication and growth. If organisms specifically tightly regulate the translation and transcription of these genes with for example checkpoints and/or negative feedback loops, cancer risk is mitigated.

Increased elimination

4. Increased immune policing of cancer cells: This relates to an increased ability to specifically detect cells that have undergone dysplasia.
5. Increased immune policing of cells with driver mutations: This engages an enhanced ability to target proto-tumors that have begun to accumulate the catenation of mutations responsible for carcinogenesis but have not yet acquired whole quorum that is necessary.

The first three tend to revolve around larger animals enjoying a lower unit mutation rate (Nunney, 2020; Plutynski, 2022) either intrinsically or as a function of tumor suppressor genes. All such genre of hypotheses were undermined by the empirical work of Cagan et al (Cagan et al., 2022). The group found no statistically significant correlation between body size and genome mutation rate across the whole gamut of species varying in size by a factor of 40,000. Even with the tumor suppressor theory; tumour suppressor gene amplification has tended to been found predominantly in certain extreme longevous animals (Caulin et al., 2015). It appears a stochastic or idiosyncratic evolutionary motif rather than a paradigm consistently reproduced in nature to counteract the apparently increased risk of carcinogenesis of multicellularity (Caulin et al., 2015). The immune policing paradigm is essentially a manifestation of increased elimination.

The insolubility of the riddle

The insolubility of the paradox lies in the fact that it comprises two moieties, which are often conflated. The chronology of the catenation of epiphanies that led Peto to unearth his paradox compounds the complexity. Peto first noted and then reported in 1975 that the probability of cancer correlated with the duration of exposure to the carcinogen (Peto et al., 1975; Tollis et al., 2017). In 1977 he then mused as to why humans and mice have the same cancer risk when the former has 1000 more cells and has a lifespan 30-fold greater than the murine counterpart. Larger animals do indeed tend to have greater longevity than smaller species. Thus quantitative attempts to resolve the paradox have had to contend with the fact that larger animals have more cells and a greater lifespan and yet have equivalent cancer risk to smaller more ephemeral species. The oversight is to assume that there is one solution to both phenomena.

In reality the paradox comprises two questions.

1. Why do larger animals not have a greater cancer risk than their smaller counterparts given they have more cells?
2. Larger species also tend to be longer-lived animals. Why is this increasing longevity not associated with a higher cancer risk?

The error thus far has been to conflate both questions into a unitary "Peto's paradox" and thence to attempt to find or assume there is a single solution for both questions and hence a single solution to the Paradox.

Cagan's catechesis

Cagan's work is seminal in the resolution of the paradox (Cagan et al., 2022). He discriminated between the two limbs of the paradox. Cagan's group first showed no statically significant correlation between body size and mutation rate. However he did demonstrate that longer-lived animals enjoy a lower mutation rate. It appears longer-lived species have a lower mutation rate. Hence the second limb is solved. It is now easier to attend to the first limb as to why larger animals have equivalent cancer risk to their smaller counterparts.

Immunosurveillance

Cagan's work largely excludes the possibility that the greater cellularity of larger animals elicits a diminution in mutagenic rate. This eliminates Nunney model hypotheses 1-3 (Nunney, 2020). There remains one class of theory, that of increased immune patrol. Nunney qualitatively explored this but excluded it as improbable as it would result in astronomically high levels of efficiency by the immune system. However Nunney attempted to use the immune patrol model to explain both components of the Peto paradox namely why large animals have comparable cancer rates to their more diminutive counterparts and why those with greater longevity have the same cancer probabilities as species with briefer lifespans. However the latter phenomenon has now been accounted for by Cagan. If immunity were to explain both observations, clearly superhuman levels of immunity would be required. However it need only explain lack of correlation with species size and cancer probability. Here we postulate that as species increase in body size, so too does the quantity of anti-cancer immunocytes and anti-tumor immune infrastructure. These cells are not more efficient per se, but increase in number commensurate with cells. Consider one police officer monitoring a group of 10 individuals. Now consider if

the number of individuals increased to 100 individuals. If there were 10 police officers each would be observing ten individuals. An analogous feature is seen in animals across the size spectrum. The medium of cancer surveillance is via immunocytes in the blood. One remarkably consistent feature across the whole gamut of species is blood volume per unit mass. Body mass and blood volume correlate with an r (Mammals and mutations, life span, cancer risk, 2022) coefficient of 1; across species varying in body mass by a factor of over 10,000 (Lindstedt and Schaeffer, 2002). Hence immune-surveillance increases in manner commensurate with species size.

The latest evidence demonstrates tumorigenesis is critically dependent upon the conflicting processes of carcinogenesis and immuno-eradication. Hoyos et al. demonstrated that mutations of the P53 gene most likely to result in cancer were those that maximized oncogenic potential and yet minimized immunogenicity of resultant neoantigens (Hoyos et al., 2022). Onco-protection is not a tangential function of immunity but a germane function. Every facet of immunity including innate and adaptive immunity are involved in the process (Pratt and Milner, 2023; Innate immune barrier against oncogenic transformation, 2025; Roerden and Spranger, 2025).

The cardinal role of immunosurveillance in onco-prevention is also evidenced by clinical practice where some of the most potent chemotherapies are the immune checkpoint blockage drugs. In order to evade immunity cancer cells activate immune checkpoints that deactivate immunity and temper its ability to recognize tumor antigens. The most common targets for cancer cells are the PD1 and CTLA-4 pathways. Anti-tumor antibody therapies bind to PD1 and CTLA-4 abrogating tumor-mediated deactivation (Kroemer et al., 2024). It noteworthy that, in their tumoricidal, action these antibodies do not bind virulent assault tumor antigens, but merely restart a decommissioned immune systems, whose empiric function is tumor clearance. Similarly chimeric antigen receptor T cell therapy (CAR-T) mimics this process by creating T cells specifically against tumor antigens (Uslu and June, 2024).

The role of immunity in oncogenesis is pervasive. Mutations to Human Leukocyte Antigen genes (HLA), encoding the membrane proteins responsible for presenting antigens to leucocytes, directly affects cancer risk (Krishna et al., 2024). The greatest threat to cancer initiation and growth is host immunity. Hence cancer cells often adopt the most extreme methods to nullify immunity. This includes the almost unbelievable kleptomity (theft of mitochondria) and substitution with defective mitochondria into immune cells (Ikeda et al., 2025).

The primacy of immune-surveillance is equally highlighted by the heliovaccination (solar vaccination) hypothesis that postulates that sunlight creates cancer neoantigens in the skin which are eliminated by the immune system, increasing immunity to cancer, thus reducing the risk in later life. This accounts for the strong and persistent negative correlation of between increasing UV exposure and cancer risk unexplained by vitamin D (Uzoigwe, 2020).

Peto's paradox is insoluble if one seeks a single solution. However it comprises two conundra with two distinct solutions.

Discussion

Immuno-surveillance is necessarily operative as a means of onco-protection, as underlined by the increasing body of evidence highlighting the indispensable nature of the effect. Further Cagan et al. elegantly demonstrated that longevity is associated with a decrease in mutation rate. Notwithstanding these fundamentally operative mechanisms, numerous other means have evolved stochastically and idiosyncratically to prevent tumorigenesis. Perillo et al. in a comprehensive and instructive systematic review, identify almost 150 distinct adaptive means of onco-protection, with numerous cellular players implicated (Perillo et al., 2024). These, although numerous, must be placed in context. There are currently possibly 10 million extant known different species inhabiting the earth, but only 150 longevity-tumor suppressor mechanisms identified to date. This paradigm remains very much idiosyncratic. In any event the underlying principle persists immutable. Each of these 150 adaptive mechanisms should initially be applied to one limb of Peto's paradox: either the size and tumor risk conflict or the longevity and cancer risk conundrum. If applied to both they may be found wanting. Further these additional seno- and onco-preventative phenotypes do not detract from the empiric ubiquitous Cagan-immunity binary solution to the Peto's paradox.

The sedulousness and lucubration with which natural selection has sought to combat tumorigenesis is *prima facie* antithetical as tumors occur principally after the reproductive years. Such attention from natural selection is generally reserved for traits that impact upon reproductive success. With this in mind a paradigm shift is required in Peto's paradox, oncogenesis and ageing itself. To maximize reproductive success organisms must ensure that they remain at their physiological apogee with no diminution in fitness during reproductive years and parenting period. Hence there must necessarily be healthy ageing. A prodigious species and individual must advance through its years of reproduction with no decroissance in neither nubility nor physiological fitness, if it is to maximize reproductive success. The primary objective is therefore healthy ageing. A necessary sequitur of that is that once these years are completed there will be a protracted period of non-reproductive longevity characterized by a decline in function during which onco-genesis may occur. If a species wants to totally eliminate the risk of cancer or deficits in fitness during the entirety of the window of fecundity, an inevitable consequence or by-product is an elongated post-fecund period of survival. If longevity coincided with the reproductive window there would be an inevitable decline during the years of courtship, reproduction and parenting; compromising reproductive success. Instantaneous post-reproductive paracme is impossible without a decline during the years of reproduction. Hence longevity and onco-protection are merely by-products or exaptations and/or spandrels of the ultimate objective, which is healthy ageing. The evidence for this conclusion is compelling. Immunocytes specifically remove senescent cells, even those that do not necessarily exhibit traits of carcinogenesis (Prieto et al., 2023).

Senescence is a surrogate for onco-potential. Immunity and ageing are intimately linked (Abbott, 2024).

A spandrel is a by-product of another evolutionary adaptation. An exaptation is a phenotype that evolves for one purpose but latter then serves another purpose (Gould, 1997). In humans where grand-parenting plays a critical role, adaptations to prevent oncogenesis and promote longevity may have evolved for the purpose of healthy ageing but now serve purpose of enabling and facilitating the nurturing role of grandparents.

Peto's paradox is insoluble if one seeks a single solution. It comprises two conundra with two distinct solutions. Any "solution" must be titrated against each conundrum singularly or the paradox is insuperable. However in many ways the solutions are a distraction; as we are posing the wrong question with the paradox. Natural selection had no interest in preventing cancer or ageing *per se* as they are features of post-reproductive window. Rather its only interest lies in maximizing and guaranteeing peak fitness with no decline or diminution in this for the entirety of the fecund years. A necessary result, exaptation or spandrel is longevity and onco-protection.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

CU: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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