initiatives have emerged to support such efforts. Continuing to diversify in this way[14] will accelerate our understanding of how common and rare genetic variants combine with environmental factors to shape individual risk for mental illness.

Conrad O. Iyegbe and **Paul F. O'Reilly** are at the Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA.
e-mails: conrad.iyegbe@mssm.edu; paul.oreilly@mssm.edu

1. Gibson, G. *Nature Rev. Genet.* **13**, 135–145 (2012).
2. Trubetskoy, V. *et al. Nature* **604**, 502–508 (2022).
3. Singh, T. *et al. Nature* **604**, 509–516 (2022).
4. Mullins, N. *et al. Nature Genet.* **53**, 817–829 (2021).
5. Demontis, D. *et al. Nature Genet.* **51**, 63–75 (2019).
6. Cross-Disorder Group of the Psychiatric Genomics Consortium. *Cell* **179**, 1469–1482 (2019).
7. The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. *Nature Genet.* **43**, 969–976 (2011).
8. Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature* **511**, 421–427 (2014).
9. Singh, T. *et al. Nature Neurosci.* **19**, 571–577 (2016).
10. Kaplanis, J. *et al. Nature* **586**, 757–762 (2020).
11. Palmer, D. S. *et al. Nature Genet.* https://doi.org/10.1038/s41588-022-01034-x (2022).
12. Hindley, G. *et al. Transl. Psychiatry* **11**, 466 (2021).
13. Pereira, L., Mutesa, L., Tindana, P. & Ramsay, M. *Nature Rev. Genet.* **22**, 284–306 (2021).
14. Stevenson, A. *et al. BMJ Open* **9**, e025469 (2019).

Evolution

Mutational clocks tick differently across species

Alexander N. Gorelick & Kamila Naxerova

Throughout life, cells accrue mutations. It now emerges that longer-lived animals acquire mutations at a slower rate than do short-lived species, potentially explaining why cancer risk does not increase with lifespan. **See p.517**

The animal kingdom comprises amazing diversity, ranging from small, short-lived animals to large, long-lived species. How does the risk of developing cancer manifest across these different life forms, and what are the molecular underpinnings of this? Cagan *et al.*[1] (page 517) and Vincze *et al.*[2] provide some answers.

How does cancer originate? To the best of our knowledge, it arises from a cell that has acquired a critical number of inauspicious genetic alterations. These abnormalities decouple it from the ordered cell society in which it resides, and enable a rogue existence that might eventually result in tumour formation.

If this classic model is accurate, then the probability that such a rogue cell will arise should scale with lifespan and with the number of cells in an organism's body. A blue whale has many more cells and lives much longer than does a mouse, so surely a whale is at higher risk of developing cancer than a mouse is. Strangely, this is not so. The surprising lack of association between body size, lifespan and cancer risk is named Peto's paradox[3], after epidemiologist Richard Peto, who mused about this in 1977.

The two latest reports provide new food for thought about this paradox. Vincze *et al.* prove Peto right through an analysis of mortality for 191 species in zoos, and confirm that animals with larger bodies or longer lives are not more likely to die of cancer than are smaller animals or animals with shorter lifespans. Cagan and colleagues study the mechanisms underlying Peto's paradox by investigating how rapidly cells in different animal species acquire mutations (Fig. 1). The authors conclude that cells in long-lived animals mutate much more slowly than do cells in short-lived species, providing a possible explanation for why cancer risk does not necessarily scale with lifespan.

Comparing genome-wide mutation rates across species is not a simple undertaking. Accurately measuring mutations in single cells poses substantial technical difficulties, and mutations in large populations of cells are hard to detect if the constituent cells are genetically diverse. Cagan *et al.* devised an inspired solution to this problem by choosing to sequence a particularly suitable cell population across 16 animal species. The authors focused on structures in the colon called crypts, which are tiny folds consisting of gut epithelial cells. These cells all have a common ancestral cell that existed a relatively short time ago compared with the species' lifespan. Therefore, sequencing genomes from crypts provides an excellent estimate of the number of
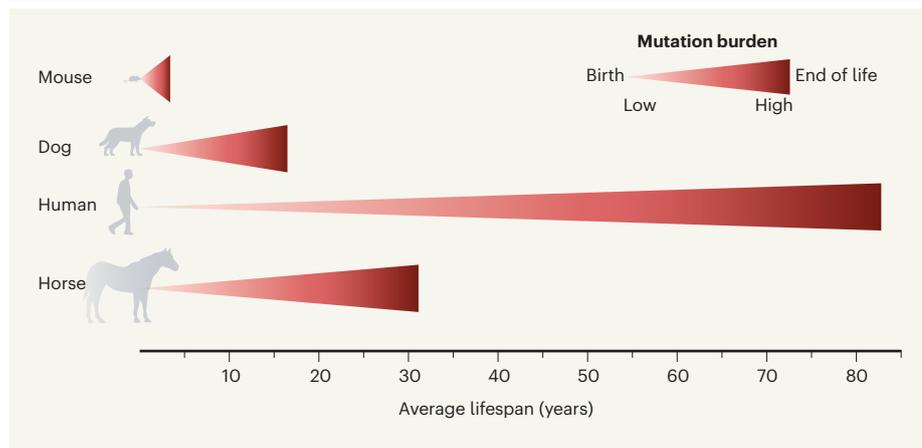
News & views

Figure 1 | Lifespan and the accumulation of mutations across species. If the number of mutations in a cell (the mutation burden) drives the risk of developing cancer, then animals that live longest and have the most cells should be the most likely to die of cancer. However, as confirmed by Vincze *et al.*[2], this is not the case, and this puzzle is known as Peto's paradox[3]. Cagan *et al.*[1] gathered data that enabled them to estimate the mutation rate (the number of mutations per cell per year) for 16 animal species, 4 of which are shown here. The authors found that species with shorter lifespans accrue mutations at higher rates compared with long-lived species, resulting in similar end-of-life mutation burdens per cell for different species. This finding partially explains Peto's paradox. Long-lived species also tend to be larger, and therefore might have evolved further mechanisms for combating cancer, such as extra copies of genes that function to prevent tumour formation.

mutations present in the ancestral cell.

Previous work[4] established that the number of mutations in human crypts increases by a constant amount every year. Cagan and colleagues find that the same is true for other species: their data for individual crypts are consistent with the number of mutations increasing in a linear fashion over an organism's lifetime. Moreover, the processes that introduce mutations into the genome do not seem to differ substantially between species. The big surprise came when the authors compared the total number of mutations acquired by the genomes of individual crypts every year. This number varied strikingly, from approximately only 47 mutations in individual human crypts to 796 in mice, an almost 17-fold difference. This difference is staggering, given the large overall similarities between human and mouse genomes.

Cagan *et al.* investigated which life-history traits correlate with crypt mutation rate (the number of new mutations per year per crypt) across species. The authors considered several species characteristics, including adult body mass, litter size and physiological measurements such as basal metabolic rate. The most striking correlation was with lifespan. Longer-lived animals acquired few mutations every year and shorter-lived animals acquired many mutations, which meant that the total number of mutations at the end of an animal's life was roughly similar across species.

These results are thought-provoking, particularly when taken together with Vincze and colleagues' findings that lifespan does not seem to have a major role in shaping cancer risk. Instead, Vincze *et al.* noted that

carnivorous mammals that consume the raw meat of other mammals are at elevated risk of dying from cancer, perhaps owing to the transmission of cancer-promoting viruses through such a diet.

The pieces of the puzzle seem to fit together well: longer-lived animals have a low mutation rate, which brings their risk of cancer mortality down to levels similar to those of shorter-lived species. So, is Peto's paradox solved? Partially, yes. However, an explanation for the role of body size is missing. Even if the per-cell mutation number at the end of life is similar across species with different lifespans, longer-lived species tend to be larger (and have more cells) and thus would be expected to have a higher cancer risk than smaller species have. This discrepancy might be explained by the evolution of extra mechanisms to reduce cancer risk in larger-bodied species. For example, elephant genomes[5] have 20 copies of the powerful anticancer gene *TP53* (at least some of which are partially functional[6]).

The findings made by Cagan *et al.* raise another intriguing question. Is death from cancer the only selective pressure affecting mutation rates? Other than increasing cancer risk, the accumulation of mutations over an organism's life is hypothesized to impair cellular function, thereby leading to organ failure and death in old age[7]. Have low mutation rates in long-lived species perhaps evolved to decelerate ageing processes in general?

Mutation rate is not the only molecular characteristic that correlates closely with lifespan: for example, higher rates of shortening of chromosomal structures called

telomeres[8] and higher protein-turnover rates[9] are observed in animals that have shorter lifespans. The latter is less clearly linked to tumour formation, potentially supporting the argument that mutation rates in long-lived species are somehow capped to delay ageing in general. However, several studies report that individuals born with genetic changes that lead to higher than normal mutation rates in various tissues do not show overt signs of accelerated ageing[10,11], which argues against a straightforward connection between the accumulation of mutations and ageing.

Cagan and colleagues propose a bold hypothesis: perhaps it is not primarily a rising number of mutations that contribute to tissue ageing, but rather an increasing prevalence of cell populations that have acquired 'selfish' mutations, which negatively affect an organ's function. Such mutations can spread within tissues by conferring an advantage to cells that carry them[12], but they might also change the cell's behaviour in ways that are disadvantageous for the organism. Evidence for such a mechanism is so far sparse, but our understanding of the evolution of cell lineages in normal and ageing tissues is only in its infancy. The work of Vincze *et al.* and Cagan *et al.* is a wonderful reminder of how much our conceptual thinking about human health and disease can be enriched by expanding our horizon to consider other species.

Alexander N. Gorelick and **Kamila Naxerova** are in the Department of Radiology and at the Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02129, USA.
e-mail: naxerova.kamila@mgh.harvard.edu

1. Cagan, A. *et al. Nature* **604**, 517–524 (2022).
2. Vincze, O. *et al. Nature* **601**, 263–267 (2022).
3. Peto, R. https://wellcomecollection.org/works/p3pm7b2e (1977).
4. Lee-Six, H. *et al. Nature* **574**, 532–537 (2019).
5. Abegglen, L. M. *et al. JAMA* **314**, 1850–1860 (2015).
6. Seluanov, A., Gladyshev, V. N., Vijg, J. & Gorbunova, V. *Nature Rev. Cancer* **18**, 433–441 (2018).
7. Kennedy, S. R., Loeb, L. A. & Herr, A. J. *Mech. Ageing Dev.* **133**, 118–126 (2012).
8. Whittemore, K., Vera, E., Martínez-Nevado, E., Sanpera, C. & Blasco, M. A. *Proc. Natl Acad. Sci. USA* **116**, 15122–15127 (2019).
9. Swovick, K. *et al. Mol. Cell. Proteom.* **20**, 100041 (2021).
10. Robinson, P. S. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.10.20.465093 (2021).
11. Robinson, P. S. *et al. Nature Genet.* **53**, 1434–1442 (2021).
12. Kakiuchi, N. & Ogawa, S. *Nature Rev. Cancer* **21**, 239–256 (2021).