Letter to the Editor

Accelerated aging and young-onset cancer risk!—are stressors of the PELICan hypothesis the missing link?

Savio George Barreto[1,2]^, Stephen J. Pandol[3]

[1]Division of Surgery and Perioperative Medicine, Department of Surgery, Flinders Medical Center, Bedford Park, Adelaide, Australia; [2]College of Medicine and Public Health, Flinders University, Adelaide, Australia; [3]Division of Digestive and Liver Diseases, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Correspondence to: Savio George Barreto, FRACS, PhD. Division of Surgery and Perioperative Medicine, Department of Surgery, Flinders Medical Centre, Bedford Park, Adelaide, South Australia 5042, Australia; College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia. Email: georgebarreto@yahoo.com; savio.barreto@sa.gov.au.

Submitted Apr 17, 2024. Accepted for publication Jul 03, 2024. Published online Aug 01, 2024.
doi: 10.21037/cco-24-56
View this article at: https://dx.doi.org/10.21037/cco-24-56

At the 2024 Annual Meeting of the American Association for Cancer Research, researchers from Washington University in St. Louis (1) postulated a hypothesis that an increase in biological age reflective of accelerated aging could play a role in early-onset (cancers occurring in adults below the age of 55 years) carcinogenesis. They examined data from 148,724 individuals within the U.K. Biobank database. Each person's biological age was calculated using the following biomarkers, including red cell distribution width, mean corpuscular volume, white blood cell count, lymphocyte proportion, blood: albumin, serum alkaline phosphatase, serum C-reactive protein, serum creatinine and serum glucose. They defined accelerated aging to be present when the person's biological age exceeded their chronological age.

The concept of accelerated aging was analysed across birth cohorts. The researchers determined that individuals born in, or after, 1965 were 17% more likely to have accelerated aging compared to those born from 1950 to 1954. Tian and colleagues (1) also studied any association between accelerated aging and the risk of young-onset cancers. In doing so, they noted that every increase in standard deviation in accelerated aging raised the risk of early-onset lung cancer, early-onset gastrointestinal cancer and early-onset uterine cancer increased by 42%, 22% and 36%, respectively. Interestingly, accelerated aging was associated with increases in the risk of late-onset uterine and gastrointestinal cancers by 23% and 16%, respectively, but had no significant risk on the development of late-onset (defined here as cancer diagnosed after age 55 years) lung cancer.

López-Otín *et al.* (2) proposed the twelve interconnected hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. Polsky *et al.* (3) recently reviewed the evidence on the activation of the neurobiological response cascade following exposure to chronic adverse conditions. From this data, they proposed an integrated conceptual model on stress-induced biological aging which speaks to repeated and/or prolonged stressful life experiences accelerating aging. Accelerated aging, in turn, is associated with an increased risk of early onset of age-related disease. The findings of Tian *et al.* (1) provide the first evidence one possible mechanism (i.e., accelerated aging) for the role of stressors on the development of early-onset cancer. The PELICan hypothesis (4,5) postulated to explain the rise in early- or young-onset cancers is based on the role of stressors at two critical time periods in an individual's life, namely, the perinatal and adolescent years, resulting in epigenetic modifications. This hypothesis seems to explain accelerated aging resulting from repeated

^ ORCID: 0000-0002-0996-1487.

stressors (3) and serve as the missing link as to why cancer is on the rise in young people.

Proving the PELICan hypothesis remains a priority for multiple reasons. It represents a major paradigm shift in our understanding of cancer from a genetic disease to one that may have a foundation in psycho-socio-economic factors. It also presents the opportunity to identify a subgroup of individuals considered high-risk for development of early-onset cancers who could be offered novel non-invasive screening tests. This would enable early detection of cancer at a stage when cure would be possible. It presents opportunities to reduce the risk of young-onset cancers by intervening in the perinatal period, as well as in child-, and adulthood. Finally, considering the recent findings by Tian *et al.* it presents a novel opportunity to administer therapies targeting the Hallmarks of aging (2) to obviate the risk of future cancer formation.

Acknowledgments

Funding: This research was supported by the US National Institutes of Health (R01 AA024464, P01 DK098108, P50 AA0119991, U01 DK108314 to S.J.P.), the US Department of Defense (W81XWH1910888 to S.J.P.), Flinders Foundation Grant (49358025 to S.G.B.), NHMRC Ideas Grant (2021009 to S.G.B.), Pankind 21.R7.INV. CB.UOSA.6.2 (to S.G.B.) and funds from the CUREator Scheme via Brandon BioCatalyst (to S.G.B.).

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article has undergone external peer review.

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-24-56/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-24-56/coif). S.G.B. serves as an unpaid editorial board member of *Chinese Clinical Oncology* from December 2022 to November 2024. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Tian R, Tica S, Hong D, et al. 846/19 - Rising accelerated aging in recent generations associated with elevated risk of early-onset cancers. American Association for Cancer Research Annual Meeting; 7th April, 2024; San Diego, USA; 2024.
2. López-Otín C, Blasco MA, Partridge L, et al. Hallmarks of aging: An expanding universe. Cell 2023;186:243-78.
3. Polsky LR, Rentscher KE, Carroll JE. Stress-induced biological aging: A review and guide for research priorities. Brain Behav Immun 2022;104:97-109.
4. Barreto SG, Pandol SJ. Young-Onset Carcinogenesis - The Potential Impact of Perinatal and Early Life Metabolic Influences on the Epigenome. Front Oncol 2021;11:653289.
5. Barreto SG. We Asked the Experts: Providing the Road Map to Uncovering the Pathophysiology of Young-Onset Cancer to Guide Treatment and Preventive Strategies. World J Surg 2020;44:3212-3.

Cite this article as: Barreto SG, Pandol SJ. Accelerated aging and young-onset cancer risk!—are stressors of the PELICan hypothesis the missing link? Chin Clin Oncol 2024;13(4):63. doi: 10.21037/cco-24-56