Centenarians may hold a key to continued rise of human longevity

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A recent perspective article (1) on human longevity focuses on socioeconomic standards and health care. In our opinion the authors could have considered a number of distinct characteristics displayed by centenarians. This is important because these characteristics, when viewed together, provide evidence that slow aging is influenced by genetics and comes with a unique disease pattern and a need for special medical care.

First, many aging-associated diseases seem to cause less morbidity and mortality among centenarians; e.g., cancer incidence increases until about 85 y and then gradually and markedly declines to 0 to 4% (2–4). Second, stem cell division rate is reduced among old people (5) and has been shown to be associated, possibly in a causal manner, with both cancer (5) and atherosclerosis (6). Third, centenarians' longevity may be due to a distinct genetic constitution (in addition to chance and lifestyle), as judged by accumulating data suggesting that aging is a polygenic trait (7), including a recent report on selection during human evolution against late-onset common diseases (8).

These characteristics prompted us to construct a mathematical model involving a simulated population with heterogeneity in the aging rate. We find that a constitutional and normally distributed death risk growth factor results in a curve that fits very well with real-life data on Swedish women (Fig. 1). The latter data points make up a typical example of a real-life population with death risk increasing with much the same factor for every year of advancing age, but with this factor becoming reduced at very high age (9). While we acknowledge that chance and lifestyle variation within a population can produce a similar curve, we argue that our model also indicates that the aging rate can vary between individuals, for example in a normal distribution manner. Furthermore, we modeled three subpopulations illustrating how slow-aging individuals become enriched during increasing age (Fig. 2). The most slowly aging 0.2% of the total population will dominate at about 112 y.

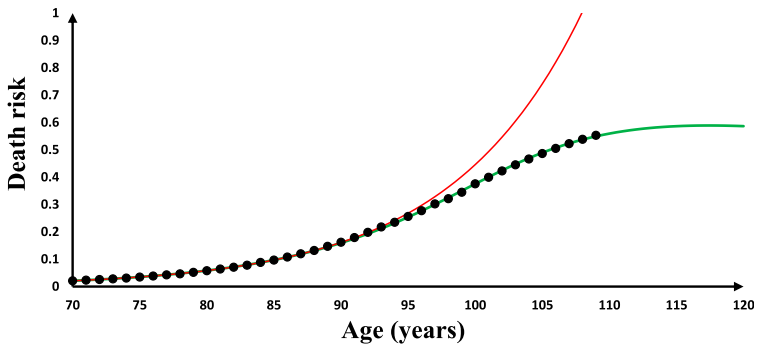

Fig. 1. A mathematical model with normally distributed death risk growth factor produces a curve similar to real-life data on women in Sweden accessed from the Human Mortality Database (https://www.mortality.org). The death risk denotes the risk of dying during the coming year. Among the Swedish women, the death risk increases each year from 0.021 at age 70 y by a factor of about 1.107 until the yearly growth factor starts to decrease at an age of about 95 y to approach 1 at 110 y and apparently reaches a plateau with death risk about 0.6 (black dots). In the model population (green line), death risk is taken to be 0.021 at age 70 y and the death risk growth factor is normally distributed with mean of 1.107 and SD of 0.0091. The red line illustrates the curve pattern of a population with all individuals having the same death risk growth factor.

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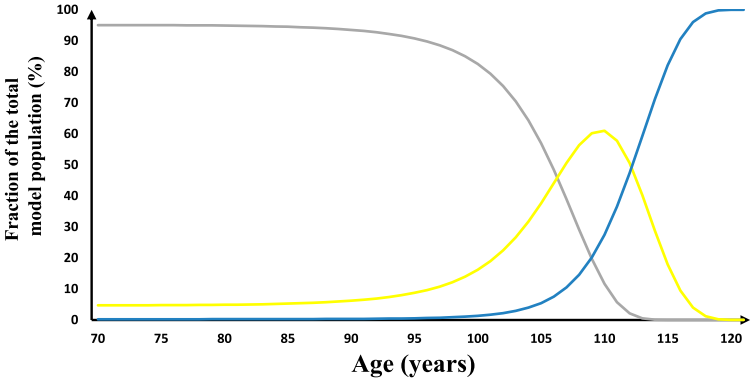

Fig. 2. Gradual selection over time of slowly aging individuals. Three arbitrarily derived subpopulations of the normally distributed model are shown: 1) 0.2% of the total population have the lowest death rate growth factor (blue line), 2) 4.7% the next-lowest level (yellow line), and 3), the remaining 95% comprise all remaining individuals with higher death risk growth factor (gray line). The 95% majority becomes the minority at 106 y, and the most slowly aging 0.2% minority group will come to dominate at about 112 y.

Standard health care may not fully meet the needs of very old people. For example, cancer in centenarians is relatively indolent with less metastasis (2, 4), and the superior response rate to checkpoint blockade among the oldest patients (10) suggests that immunotherapy could be preferable to cytotoxic agents. If a distinct pattern of disease and optimal therapy is coupled with a slow-aging constitution, then it is worth pointing out that the aging rate typical for centenarians, at present making up less than 1‰ in developed countries, is a constitutional characteristic of a much higher number of individuals at younger ages.

In conclusion, there is evidence suggesting that aging is a normally distributed trait and that special medical care of slowly aging people has potential to make them live longer and for more of them to even become centenarians.

1 J. W. Vaupel, F. Villavicencio, M.-P. Bergeron-Boucher, Demographic perspectives on the rise of longevity. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2019536118 (2021).
2 K. C. Suen, L. L. Lau, V. Yermakov, Cancer and old age. An autopsy study of 3,535 patients over 65 years old. *Cancer* **33**, 1164–1168 (1974).
3 S. L. Andersen, P. Sebastiani, D. A. Dworkis, L. Feldman, T. T. Perls, Health span approximates life span among many supercentenarians: Compression of morbidity at the approximate limit of life span. *J. Gerontol. A Biol. Sci. Med. Sci.* **67**, 395–405 (2012).
4 N. Pavlidis, G. Stanta, R. A. Audisio, Cancer prevalence and mortality in centenarians: A systematic review. *Crit. Rev. Oncol. Hematol.* **83**, 145–152 (2012).
5 C. Tomasetti *et al.*, Cell division rates decrease with age, providing a potential explanation for the age-dependent deceleration in cancer incidence. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 20482–20488 (2019).
6 A. Heyde *et al.*, Increased stem cell proliferation in atherosclerosis accelerates clonal hematopoiesis. *Cell* **184**, 1348–1361.e22 (2021).
7 D. Melzer, L. C. Pilling, L. Ferrucci, The genetics of human ageing. *Nat. Rev. Genet.* **21**, 88–101 (2020).
8 S. Pavard, C. F. D. Coste, Evolutionary demographic models reveal the strength of purifying selection on susceptibility alleles to late-onset diseases. *Nat. Ecol. Evol.* **5**, 392–400 (2021).
9 L. A. Gavrilov, N. S. Gavrilova, New trend in old-age mortality: Gompertzialization of mortality trajectory. *Gerontology* **65**, 451–457 (2019).
10 G. Ben-Betzalel *et al.*, Immunotherapy comes of age in octagenarian and nonagenarian metastatic melanoma patients. *Eur. J. Cancer* **108**, 61–68 (2019).