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Tying it all together: telomeres, sexual size dimorphism and the gender gap in life expectancy

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Summary The classic explanation that women outlive men solely due to hormonal and lifestyle differences, does not withstand a critical analysis. In developed countries, the average gap in life expectancy between the sexes is 7 years. It has widened over the last decades, despite the trend of women copying the 'unhealthy' lifestyle of men. Estrogen levels in postmenopausal women are virtually identical to estrogen levels in males and can hardly explain the discrepancy. Furthermore, testosterone got its bad reputation from one study on mentally retarded men, which has to be interpreted with caution. However, sexual size dimorphism with men being the larger sex in conjunction with the limited replication potential of human somatic cells might account for higher mortality rates in males, especially at old age. The hypothesis, as presented here, is based on the well-known concept of a cellular mitotic clock, which was discovered by Leonard Hayflick almost half a century ago. The underlying counting mechanism, namely the gradual erosion of chromosome ends (telomeres) due to the end replication problem of linear DNA molecules, was first described by Alexey Olovnikov in 1971 and with minor modifications has become a widely accepted paradigm. In a recent Lancet study, an inverse correlation between mean telomere length and mortality in people has been found. In this and two other studies, it was confirmed that males do have shorter telomeres than females at the same age. This is almost certainly a consequence of men being usually taller than women, although nobody has done an investigation yet. Clearly, a larger body requires more cell doublings, especially due to the ongoing regeneration of tissues over a lifetime. Accordingly, the replicative history of male cells might be longer than that of female cells, resulting in the exhaustion of the regeneration potential and the early onset of age-associated diseases predominantly in large-bodied males. Inherited telomere length variation between unrelated individuals might have obscured a clear correlation between body height and mortality, leading to conflicting results in some studies. Finally, I propose that the secular height increase over the last decades, of about 2.5 cm per generation in the western world, has to be blamed for the widening of the gender gap in life expectancy.

Introduction

The worldwide phenomenon of higher life expectancy for women, although generally acknowledged, is still an unsolved puzzle. In 1998, according to the US Census Bureau, the average gap in life expectancy at birth between the sexes was 7 years in developed countries and 3 years in developing countries [1]. Even though more boys than girls are born in all countries, middle-aged women start to outnumber men and the female advantage increases with age.

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While risky behavior, unhealthy lifestyle (alcohol, tobacco) and hormonal differences might have contributed to higher male mortality rates, they cannot entirely explain the phenomenon. Risky behavior in males for example cannot account for the discrepancy of mortality rates beyond the age of 60, but at that point men are twice as likely to die as women [2], mainly due to cardiovascular disease and cancer [1]. In addition, women have been increasingly adopting the 'unhealthy' lifestyle of men in the last 40 years or so, but in most developed countries the gender gap has still widened [1]. This leaves us with the hormonal differences. In 1969, Hamilton published data about the median life span of castrated men in comparison to intact men (although mentally ill), who were inmates at the same hospital. He found a 13.6 year difference in lifespan [3]. Paradoxically, median lifespan in the control group was very low. A median life span of 55.7 years, as reported in this paper, would match the known data of that time, if it were life span at birth, but Hamilton collected his data from a preselected group. After all the participants must have reached a certain age to become inmates at a hospital for mentally retarded. Since infant and early childhood mortality was still incredibly high during that time, median life span is expected to be much higher in this preselected group. So the only thing he proved was that testicular hormones are particularly harmful to mentally retarded men incarcerated in US state mental hospitals in the early 20th century. Nevertheless, testosterone has been regarded as a 'killer' since. Although, a study on biographical data of castrated singers compared to intact male singers born between 1581 and 1858 did not reveal any significant difference in mean life span. These data published in *Nature* in 1993 show that prepubertal removal of the testes had no influence on the longevity of men [4].

In contrast to the allegedly unhealthy testosterone, estrogen is generally considered as life prolonging. But even if estrogen would have a positive impact on life expectancy, estrogen levels in postmenopausal women are on a record low, comparable to estrogen levels in males. It is hard to imagine that a hormone increases life expectancy, if it is virtually absent during the last 30 years of a woman's lifetime.

Another theory on the cause of the gender gap is based on the random inactivation of one X chromosome in female cells [5]. For X-linked diseases it has been known that having two X chromosomes provides a health advantage [5]. Since it is very unlikely that mutations in genes on the X chromosome are involved in all age-related diseases and that mutated versions of these genes occur in all men, this model might be of academic value only.

The hypothesis

Clearly, to solve the puzzle, we have to look for other gender-specific differences. Like the gender gap, sexual size dimorphism (SSD) with men being the larger sex is a worldwide phenomenon. In mammals, a strong positive correlation between SSD and male-biased mortality has been reported [6]. The authors of a research article, recently published in *Science* [7], linked large body size to a higher burden of parasitism, resulting in increased mortality rates due to infectious diseases. However, in developed countries communicable diseases account for just 5% of all deaths at age 60 [1] and cannot explain the current gender gap. But why else should tallness be deleterious?

Before answering this question, I want to give a short survey of what is known about the limited replication potential of human cells. In 1961, Hayflick and Moorhead showed that normal human somatic cells have a limited proliferative life span (replicative senescence, Hayflick limit), related not to elapsed time but to the accumulated number of cell divisions [8]. Olovnikov hypothesized that this phenomenon results from the incomplete replication at the ends of linear DNA molecules [8], and this is still the current conventional wisdom. According to the 'end replication problem', every eukaryotic cell must compensate for terminal loss of DNA from chromosome ends (telomeres), because DNA polymerases are incapable of copying the 3′ ends of linear DNA molecules. To avoid the loss of critical genetic material, eukaryotic cells cap their DNA with hundreds of repetitions of a short, noncoding sequence (telomeric sequence) [9]. In germ cells and in early embryonic stem cells high levels of a specialized enzyme called telomerase preserve constant telomere lengths, but in human somatic cells low telomerase levels cannot prevent gradual shortening of telomeres, resulting in a limited proliferative life span of those cells.

Mean telomere length varies greatly between species, but seems to be relatively constant and quite narrow within a species [10]. Humans appear to be unique among long-lived primates in terms of telomere length that is telomeres in humans are very short [11]. On average, women do have longer telomeres than men at the same age [12—14], although mean telomere length at birth does not show any sex-related differences, suggesting a slower rate of telomeric attrition in women [15].

This brings us back to 'why tallness might be deleterious'. A larger body size requires more cell doublings, not only during its growth phase but even more importantly for tissue regeneration over a lifetime. Accordingly, a defined number of adult stem cells would be exhausted earlier in large humans than in small ones, supposing the proliferation capacity is limited. This leads us to the next question: Is the proliferation capacity of adult stem cells restricted? Hematopoietic stem cells (HSC) are the only adult stem cells, for which reliable data are currently available. In mice, HSCs can be serially transplanted only a limited number of times, depending on the mouse strain used [16]. In mice and humans, telomeres shorten in HSCs during a life time despite low to moderate levels of telomerase expression [16,17]. Telomere length is significantly reduced in hematopoietic cells of recipients of human bone marrow transplants [18] and the extent of reduction correlates inversely with the number of cells infused [17]. Taken together, the proliferative capacity of adult stem cells seems to be limited, probably due to the gradual shortening of telomeres to a critical threshold.

Some studies have found a positive correlation between large body size and age-associated diseases like cancer [19,20], on the other hand secular growth in the Western world during the last 100—150 years has been regarded as a marker for rising health. However, when each new generation increases by about 2.5 cm in height, it is just a matter of time until humans simply get too big [21]. (Over the last decade, T.T. Samaras and colleagues have published several articles on the inverse correlation between height and longevity, but in contrast to this paper, they do not focus on telomeres.) What we do not know is, if we already passed the critical threshold, where negative effects outweigh the benefits. What we do know though is that large-bodied men would reach the critical threshold first. Accordingly, it is reasonable to assume that the widening of the gender gap might be a consequence of men already approaching the critical limit.

It has been shown that telomere erosion contributes to age-related pathology, such as impaired wound healing, immunosenescence, vascular disease and cancer [14,22]. It does so by limiting the proliferative capacity of cells and subsequently by confining the regeneration potential of human tissues. If rapidly dividing cells somehow pass the Hayflick limit (due to e.g., mutations), chromosomes with extremely short telomeres undergo fusion-bridge-breakage cycles causing chromosomal instability [23], the hallmark of cancer. Although mean telomere length does not determine maximum lifespan in mammals [24], in long-lived species with relatively short telomeres it seems to affect mortality rates at old age [14]. As mentioned above, within a species larger individuals would be affected earlier than smaller ones, supposing identical mean telomere length. The reason why no robust correlation between height and mortality from age-associated diseases has been observed yet, might be that telomere length varies significantly between unrelated newborns [15]. Consequently, a given height could be deleterious to someone, whereas somebody else (with longer telomeres) it would not hurt at all.

Yet, women do have longer telomeres than men and women experience lower mortality rates (not only) at old age, which might be the result of their smaller body size in conjunction with the limited replication potential of adult stem cells. To test this new hypothesis, a long term study would have to be carried out, where mortality rate, height and mean telomere length at a certain age for both sexes would have to be measured and correlated.

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