



Sci. Aging Knowl. Environ., Vol. 2005, Issue 23, pp. pe16, 8 June 2005
[DOI: 10.1126/sageke.2005.23.pe16]

The **Longevity Gender Gap**: Are Telomeres the Explanation?

Abraham Aviv, Jerry Shay, Karre Christensen and Woodring Wright

The authors are at the Hypertension Research Center, the Cardiovascular Research Institute, University of Medicine & Dentistry of New Jersey, NJ Medical School, Newark, NJ 07103, USA (A.A.); Department of Cell Biology, University of Texas Southwestern Medical Center, Dallas, TX, USA (J.S. and W.W.); and the Institute of Public Health, University of Southern Denmark, Odense C, Denmark (K.C.). E-mail: avivab@umdnj.edu

Document URL: <http://sageke.sciencemag.org/cgi/content/full/2005/23/pe16>

Key words: cardiovascular disease • estrogen • **longevity gender gap** • oxidative stress • somatic cell selection • telomere • X chromosome

The **Longevity Gender Gap**

In the developed world in modern times, life expectancy at birth is some 7 years longer for women than it is for men (1). As males get older, their number tends to dwindle faster than that of women, partially because of a penchant for "risky behavior." The primary reason for the **longevity gender gap** (LGG), however, is likely to be biological [for a review, see (2)] and, although a matter of considerable debate, the roots of the LGG have far-reaching implications for human gerontology.

Aging arises from metabolic changes and associated structural impairments of somatic tissues, leading to a progressive decline in physiological function. "Successful aging" is a phenomenon marked by a lag in the onset--or slower progression--of diseases of aging, probably owing to less damage to, and more repair of, cells and tissues. By all accounts, women live longer than men, indicating that they age more successfully.

In the search for insight into successful aging and solutions to the enigma of the LGG, the following two questions are among many worth pursuing: First, is the biological component of LGG a result of gender-related hormonal differences or of differences in processes governed by cellular turnover within discrete anatomic domains of the vast somatic framework? Second, at the cellular level, what general features distinguish the aging trajectories of men and women?

Estrogen and the LGG

The predominant thinking, particularly in the cardiovascular field, has been that centrally controlled processes mediated by ovarian steroid hormones--notably estrogen--underlie the LGG (see [Pardee Review](#)). Androgens have also been implicated in increasing cardiovascular risks for men [for a review, see (3)] but have not garnered as much attention as estrogen has in diminishing cardiovascular risks in women. Proponents of estrogen suggest that it sustains somatic cell vitality and forestalls aging through a host of mechanisms. They point to the lower incidence of cardiovascular diseases in premenopausal women as evidence for the advantageous antiaging effect of estrogen, and have advocated estrogen supplementation [also known as hormone replacement therapy, or HRT (see "[Weathering the HRT Storm](#)")]] to stave off cardiovascular diseases in postmenopausal women. However, the recent discouraging findings of large-scale clinical trials aimed at gauging the effect of HRT in older women [for a review, see (4)] have dampened the enthusiasm for estrogen in the campaign against cardiovascular diseases in postmenopausal women. Such studies, however, do not exclude a role for estrogen as an antiaging agent: What they show is that several years of HRT may not be a viable solution to the problem of cardiovascular diseases in older women. Turgeon and co-workers (4) recently underscored this point by posing the following questions: "Although ovarian steroids provide a biological advantage in women before menopause, does that benefit cease along with the cessation of ovarian function? Does an advantage paradoxically become a risk when these hormones are replaced therapeutically?" There are alternatives to endocrine explanations for the longer lives experienced by women, however, such as intrinsic molecular genetic differences between somatic cells from women and men.

The Battle of the Xs

Whereas men have one Y chromosome and one X chromosome, women have two X chromosomes in each of their somatic cells. In normal females, one of the X chromosomes is stochastically [inactivated](#) during early embryogenesis [for a review, see (5)], so that no more than ~25% of genes on the inactive X chromosome are expressed (6). Newborn girls therefore have two populations of somatic cells at an approximate ratio of 50:50, exhibiting balanced mosaicism with respect to X inactivation. Two main circumstances have been linked to a skewed, or unbalanced, distribution of X inactivation in the somatic cells of human females, namely X-linked genetic diseases (7-10) such as [dyskeratosis congenita](#) and aging itself (11-15).

The unbalanced distribution of X inactivation in women carrying X-linked diseases and in normal women later in life has been ascribed to survival advantage. In an embryo, X inactivation of an allele harboring an abnormal gene produces a survival advantage for cells expressing the normal gene; thus, the mosaicism becomes skewed in favor of the normal X chromosome. In contrast, acquired age-related skewing of X-inactivated cells in apparently normal females arises not from a particular pattern of X inactivation in utero but from selection during extrauterine life of cells harboring a parental X chromosome that provides a survival advantage.

Because normal males possess one X chromosome, they have only one type of somatic cell, so there is no prospect for somatic cell selection (at least with respect to X inactivation) with advancing age. Females, in contrast, possess two cell types based on the identity of their

inactivated X chromosome--an attribute that may confer considerable survival advantage through somatic cell selection. A key factor in women's successful aging may therefore be the "survival of the fitter" between two somatic cell populations (16). This amounts to the replacement during a woman's life span of cells having an active X chromosome from one parent with cells having an active X chromosome from the other parent, should the latter cells exhibit a better ability to withstand the vicissitudes of aging. Clearly, cell types most likely to exhibit this unique form of selection are stem cells that give rise to highly proliferative cell populations (including blood cells, skin epidermal cells, and intestinal epithelial cells) in which turnover is an ongoing process throughout the human life span. Recent findings suggesting an X-linked component affecting the inheritance of telomere length (17) provide an added dimension to this idea and a potential explanation for the enigma of LGG.

Is There a Link to Telomere Length?

The progressive attrition in [telomere length](#) in replicating somatic cells is at the center of the telomere hypothesis of cellular aging (18), which proposes that telomeres behave like a "mitotic clock" by shortening with each division (see "[More Than a Sum of Our Cells](#)" and [Heist Perspective](#)). There is robust evidence that in replicating somatic cells telomeres become shorter with increased age [for reviews, see (19, 20)]. Cross-sectional population analyses of telomere length in white blood cells (WBCs) have been the main source of information regarding human telomere dynamics in vivo. As expressed in WBCs, telomere length is highly heritable (17, 21, 22), inversely correlated with age (17, 21-24), longer in adult women than men (17, 22, 23), and yet equivalent in newborn boys and girls (25). Two factors may account for the longer telomeres that are observed in women, namely estrogen and somatic cell selection.

Estrogen diminishes oxidative stress [for a review, see (26)], whose cumulative burden is fundamental to many theories of aging (see "[The Two Faces of Oxygen](#)"). Meanwhile, estrogen also stimulates the transcription of the gene encoding the telomerase [reverse transcriptase](#) enzyme that adds telomere repeats (copied from its integral [RNA component](#)) to chromosome ends, thereby curtailing or slowing down the rate of telomere erosion (19, 20). Oxidative stress, conversely, escalates telomere erosion [for a review, see (27)]. Theoretically, the ability of estrogen to up-regulate telomerase and at the same time reduce oxidative stress could account for the longer telomeres observed in women as compared with men. This effect of estrogen on telomere dynamics may be attenuated or disappear altogether in older women, but its premenopausal influence could set telomere attrition at a trajectory that maintains longer telomeres in women throughout the entire human life span. Such a possibility can readily be tested in the future by longitudinal studies of telomere attrition rates in men versus women, and in premenopausal versus postmenopausal women.

Skewed X-linked selection of somatic cells as a function of aging may be another factor behind the longer telomeres observed in women as compared with men. There is good evidence for gene variance on the X chromosome that strongly influences telomere length (17). Ninety-six percent of the combined length of telomeres in a newly formed zygote is contributed by autosomal telomeres, which suggests that factors on the X chromosome influence telomere length considerably, presumably by modulating the functional activity of telomerase or other telomere length-influencing factors. If this is the case, female cells in which a hypothetical "short telomere

allele" was active would exhibit shorter telomeres at birth in comparison with those cells in which the active X chromosome carried a "longer telomere" allele. As women age, their two somatic cell populations would be redistributed toward the population that has comparatively longer telomeres, not only because telomere length appears to be influenced by an X-linked gene or genes but also for the reason that longer telomeres denote resistance to oxidative stress. To the extent that shorter telomeres are linked to increased mortality (28) (see "[When Tips Disappear, the End is Near](#)") and decreased proliferative capacity (18), selection for cells with longer telomeres might produce greater tissue reserves and decreased mortality. It is anticipated that such selection would primarily be apparent in older women, given that the critical telomere length associated with cellular senescence is more likely to occur in a later phase of the human life span. Skewed X inactivation has been observed primarily in women older than 60 years (15), supporting this tenet.

Conclusion

Aging is a kaleidoscope of interwoven genetic and epigenetic determinants and is arguably the most complex of all complex human traits. Given that the fundamentals of aging are common to both genders, the LGG is too important to ignore in the study of human aging. Ultimately, the LGG might be a matter not only of hormonal differences between men and women but also of somatic cell selection that favors cells that are more resistant to age-related dysfunction or death.

There is as yet no persuasive evidence that directly implicates telomeres as a major determinant in human aging in the general population (see [Aviv Perspective](#)) but, based on cross-sectional analyses (20, 22-24), the rate of attrition of telomeres in WBCs is about 30 base pairs (bp) per year. The mean telomere length in women is approximately 240 bp longer than that in men (16, 21, 22), which equates to a disparity between the sexes of about 8 "telomere years," roughly the same as the observed gender **gap** in life expectancy. Such an association does not prove causality, of course, but it calls for further exploration of the links between sexual dimorphism in telomere dynamics and the LGG.

June 8, 2005

[Comment on Article](#)

References

1. 2002 World Population Data Sheet. Washington, DC: Population Reference Bureau.
2. A. B. Newman, J. S. Brach, Gender **gap** in **longevity** and disability in older persons. *Epidemiologic Reviews* **23**, 343-350 (2001).[\[Medline\]](#)
3. P. Y. Liu, A. K. Death, D. J. Handelsman, Androgens and cardiovascular diseases. *Endocrine Rev.* **24**, 313-340 (2003).[\[Abstract/Free Full Text\]](#)
4. J. L. Turgeon, D. P. McDonnell, K. A. Martin, P. M. Wise. Hormone therapy: Physiological complexity belies therapeutic simplicity. *Science* **304**, 1269-1273 (2004).[\[Abstract/Free Full Text\]](#)
5. C. J. Brown, W. P. Robinson, The causes and consequences of random and non-random X

- chromosome inactivation in humans. *Clin. Genet.* **58**, 353-363 (2000). [\[CrossRef\]](#)[\[Medline\]](#)
6. L. Carrel, H. F. Willard, X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature* **434**, 400-404 (2005). [\[CrossRef\]](#)[\[Medline\]](#)
 7. J. E. Parrish, A. E. Scheuerle, R. A. Lewis, M. L. Levy, D. L. Nelson, Selection against mutant alleles in blood leukocytes is a consistent feature in incontinentia pigmenti type 2. *Hum. Mol. Genet.* **11**, 1777-1783 (1996). [\[CrossRef\]](#)
 8. E. R. Fearon, J. A. Winkelstein, C. I. Civin, D. M. Pardoll, B. Vogelstein, Carrier detection in X-linked agammaglobulinemia by analysis of X-chromosome inactivation. *N. Engl. J. Med.* **316**, 427-431 (1987). [\[Abstract\]](#)
 9. J. Goodship, J. Carter, T. Espanol, Y. Boyd, S. Malcolm, R. J. Levinsky, Carrier detection in Wiskott-Aldrich syndrome: Combined use of M27 beta for X-inactivation studies and as a linked probe. *Blood* **77**, 2677-2681 (1991). [\[Abstract\]](#)
 10. T. J. Vulliamy, S. W. Knight, I. Dokal, P. J. Mason, Skewed X-inactivation in carriers of X-linked dyskeratosis congenita. *Blood* **90**, 2213-2216 (1997). [\[Abstract/Free Full Text\]](#)
 11. L. Busque, R. Mio, J. Mattioli, E. Brais, N. Blais, Y. Lalonde, Nonrandom X-inactivation patterns in normal females: Lyonization ratio varies with age. *Blood* **88**, 59-65 (1996). [\[Abstract/Free Full Text\]](#)
 12. L. Tonon, G. Bergamaschi, C. Dellavecchia, V. Rosti, C. Lucotti, L. Malabarba, Unbalanced X-chromosome inactivation in haemopoietic cells from normal women. *Br. J. Haematol.* **102**, 996-1003 (1998). [\[CrossRef\]](#)[\[Medline\]](#)
 13. K. Christensen, M. Kristiansen, H. Hagen-Larsen, A. Skytthe, L. Bathum, B. Jeune, X-linked genetic factors regulate hematopoietic stem-cell kinetics in females. *Blood* **95**, 2449-2451 (2000). [\[Abstract/Free Full Text\]](#)
 14. R. E. Gale, A. K. Fielding, C. N. Harrison, D. C. Lynch, Acquired skewing of X-chromosome inactivation patterns in myeloid cells of the elderly suggests stochastic clonal loss with age. *Br. J. Haematol.* **98**, 512-519 (1997). [\[CrossRef\]](#)[\[Medline\]](#)
 15. I. Sandovici, A. K. Naumova, M. Leppert, Y. Linares, C. Sapienza, A longitudinal study of X-inactivation ratio in human females. *Hum. Genet.* **115**, 387-392 (2004). [\[Medline\]](#)
 16. K. Christensen, K. H. Orstavik, J. W. Vaupel, The X chromosome and the female survival advantage: An example of the intersection between genetics, epidemiology, and demography. *Ann. N.Y. Acad. Sci.* **954**, 175-183 (2001). [\[Abstract/Free Full Text\]](#)
 17. T. S. Nawrot, J. A. Staessen, J. P. Gardner, A. Aviv, Telomere length and possible link to X chromosome. *Lancet* **363**, 507-510 (2004). [\[CrossRef\]](#)[\[Medline\]](#)
 18. C. B. Harley, H. Vaziri, C. M. Counter, R. C. Allsopp, The telomere hypothesis of cellular aging. *Exp. Gerontol.* **27**, 375-382 (1992). [\[CrossRef\]](#)[\[Medline\]](#)
 19. W. E. Wright, J. W. Shay, Historical claims and current interpretations of replicative aging. *Nat. Biotechnol.* **20**, 682-688 (2002). [\[CrossRef\]](#)[\[Medline\]](#)
 20. J. M. Wong, K. Collins, Telomere maintenance and disease. *Lancet* **362**, 983-988 (2003). [\[CrossRef\]](#)[\[Medline\]](#)
 21. P. E. Slagboom, S. Droog, D. I. Boomsma, Genetic determination of telomere size in humans: A twin study of three age groups. *Am. J. Hum. Genet.* **55**, 876-882 (1994). [\[Medline\]](#)
 22. E. Jeanclos, N. J. Schork, K. O. Kyvik, M. Kimura, J. H. Skurnick, A. Aviv, Telomere length inversely correlates with pulse pressure and is highly familial. *Hypertension* **36**, 195-200 (2000). [\[Abstract/Free Full Text\]](#)
 23. A. Benetos, K. Okuda, M. Lajemi, M. Kimura, F. Thomas, J. Skurnick, Telomere length as an indicator of biologic aging: The gender effect and relation with pulse pressure and pulse wave

velocity. *Hypertension* **37**, 381-385 (2001). [[Abstract/Free Full Text](#)]

24. S. Brouillette, R. K. Singh, J. R. Thompson, A. H. Goodall, N. J. Samani, White cell telomere length and risk of premature myocardial infarction. *Arterioscler. Thromb. Vasc. Biol.* **23**, 842-846 (2003). [[Abstract/Free Full Text](#)]

25. K. Okuda, A. Bardeguéz, J. P. Gardner, P. Rodriguez, V. Ganesh, M. Kimura, Telomere length in the newborn. *Pediat. Res.* **52**, 377-381 (2002). [[CrossRef](#)][[Medline](#)]

26. A. Aviv, Telomeres, sex, reactive oxygen species, and human cardiovascular aging. *J. Mol. Med.* **80**, 689-692 (2002). [[CrossRef](#)][[Medline](#)]

27. T. von Zglinicki, Replicative senescence and the art of counting. *Exp. Gerontol.* **38**, 1259-1264 (2003). [[CrossRef](#)][[Medline](#)]

28. R. M. Cawthon, K. R. Smith, E. O'Brien, A. Sivatchenko, R. A. Kerber, Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet* **361**, 393-395 (2003). [[CrossRef](#)][[Medline](#)]

29. The authors' research on aging and the cardiovascular system is supported by the following grants: The National Institute on Aging AG021593 (A.A.), AGP01-08761 (K.C.), and AG01228 (W.E.W.), The National Heart, Lung, and Blood Institute HL070137 (A.A.), the Nash Foundation (J.W.S.), and the New Jersey Healthcare Foundation (A.A.). W.E.W. is an Ellison Medical Foundation Scholar.

Citation: A. Aviv, J. Shay, K. Christensen, W. Wright, The **Longevity Gender Gap**: Are Telomeres the Explanation? *Sci. Aging Knowl. Environ.* **2005** (23), pe16 (2005).

Comment on this article:

Read all [Comments](#)

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

Reinhard Stindl

SAGE KE, 10 Jun 2005 [[Full text](#)]

Abstract of the 'telomere-gender **gap**' paper, published in January 2004

Reinhard Stindl

SAGE KE, 20 Jun 2005 [[Full text](#)]

[Copyright © 2005 by the American Association for the Advancement of Science.](#)