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Cardiovascular Diseases, Aging and the Gender Gap in the Human Longevity

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Abstract

This brief communication probes into the biological meaning of the gender gap in longevity and its possible ramifications to the expression of cardiovascular diseases in humans. It addresses the potential role of the estrogen and the X chromosome in the longer life span of women than men in modern societies. In addition, it links features of the reproductive and post-reproductive periods with cardiovascular diseases and longevity in women.

The Gender Gap in Longevity

There is no getting around the fact that in developed countries women live longer than men. (1). In the past, the gender gap in longevity was much smaller due to high rates of maternal death during child birth and shortly thereafter. The gender gap remains smaller in developing compared with developed countries (2). At conception the boy/girl ratio is about 3/2, while at birth this ratio drops to 1.05/1 because fetal loss is higher for males than females (3). In the USA, the man/woman ratio is 5/6 at age 65 and by age 85 it drops precipitously to 2/5 (4). Similar values have been reported for other developed nations. Thus, throughout the intra-and-extra-uterine life span the survival rate of females is considerably higher than that of males.

Risky behavior and occupational hazards of young and middle-age males partially account for the longevity gender gap, but the primary reason for it is the better somatic fitness of women than men. In modern humans, somatic fitness denotes inherent and acquired ability to ensure the individual's survival not only during the reproductive period but also the prolonged post-reproductive phase. As cardiovascular diseases (CVD) are the main cause of death in most developed countries, better somatic fitness is expressed by a slower rate of aging, and hence diminished susceptibility to CVD (5) and perhaps other aging-related diseases. The rate of aging might be modified by a host of factors that may be either genetic or environmental. For instance, in principle, cigarette smoking is an aging accelerator (6). The same may apply to excess caloric intake and a sedentary lifestyle.

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Oxidative stress and inflammation figure centrally in the biology of aging and in aging-related diseases (7,8). Diminished susceptibility of women to these diseases may therefore arise from gender-related differences in the systemic burden of oxidative stress and inflammation. However, these differences are not uniform throughout the human life span. Though pre-menopausal women are relatively protected against CVD, post-menopausal women exhibit a considerable increase in the risk for CVD, presumably due to the fall in circulating ovarian steroid hormones, particularly estrogen.

The Role of Estrogen in the Longevity Gender Gap

What then are the potential mechanisms through which estrogen engenders cardiovascular protection and increased somatic fitness during the pre-menopausal period? Estrogen exerts numerous effects among which is its ability to attenuate oxidative stress. Though estrogen metabolites may be pro-oxidant and cause DNA damage in specific target tissues such as the breast (9), in most tissues estrogen appears to diminish oxidative stress via a number of mechanisms. These include estrogen-mediated scavenging of free radicals, inhibiting free radical formation, and altering the expression and activity of key enzymes engaged in free radical metabolism (10–13). In addition, the production of nitric oxide (NO), a powerful vasodilator, is higher in pre-menopausal women than in men (14), perhaps because estrogen increases NO release from the vascular endothelium while down regulating NADPH expression (15). These estrogen-mediated effects would diminish the levels of not only free radicals but also nitrites/nitrates, which can cause considerable tissue damage. Though the biological effect of ovarian hormone supplements in post-menopausal women is a matter of controversy (16), it appears that during the pre-menopausal period endogenous ovarian steroid hormones act as anti-inflammatory, as the rise in pro-inflammatory cytokines in post-menopausal women is attributed to the fall in the levels of these hormones. (17). Thus, by reducing free radicals and nitrites/nitrates and perhaps diminishing inflammation endogenous estrogen retards the aging of the cardiovascular system during the pre-menopausal period, thereby contributing to the better somatic fitness of middle-age women than men. Interestingly, testosterone also displays anti-inflammatory properties, yet its role in CVD has received scanty attention as compared with that of estrogen (18).

The Role of the X Chromosome in the Longevity Gender Gap

Having two X chromosomes may also account for the better somatic fitness in women than men and its lasting effect is exerted not only during the pre-menopausal but also the post-menopausal period. In normal females one of the two X chromosomes is stochastically inactivated during early embryogenesis (19), so that only 25% of the genes are expressed on this chromosome (20). Thus, most normal newborn girls have two populations of somatic cells at an approximate ratio of 50:50, meaning, they exhibit balanced mosaicism with respect to X-chromosome inactivation. In contrast, elderly women often exhibit skewed mosaicism with respect to X-chromosome inactivation. In some elderly women cells with an active paternal X chromosome predominate, while in other women cells with active maternal X chromosome hold sway (21–23). Since X chromosome inactivation takes place only during early embryonic life, skewed mosaicism during extra-uterine life can only arise from the selective survival of stem cells. In some women stem cells that harbor the active X chromosome derived from the father display better survival, while in other women better survival is expressed in stem cells with the active X chromosome derived from the mother. Thus, during a woman's life span, stem cells having an active X chromosome from one parent are ostensibly being replaced with cells having an active X-chromosome from the other parent, if the latter stem cells better withstand aging. Perhaps oxidative stress is involved, as it limits, for instance, the life span of hematopoietic stem cells (24) and may act in a similar fashion on other stem cells that give rise

to highly proliferative cell populations. Therefore, stem cells that are capable of resisting oxidative stress endure while their cell mates vanish.

The Evolutionary Perspective of the Reproductive and Post-Reproductive Periods

While somatic cell selection apparently works throughout the life span of women and perhaps more so in older women, estrogen exerts its effect primarily during the reproductive period. What then is the biological meaning of the partition of the human life span into reproductive and post-reproductive years and can it explain variation in somatic fitness at the systemic level and hence variation in CVD among women?

The period of reproduction entails intense selection among members of a species, a process that facilitates the survival of the fittest. But the force of natural selection rapidly declines during the post-reproductive period (25). To reconcile aging with evolutionary principles, three major hypotheses have proposed mechanisms that causally link the reproductive with the post-reproductive periods. They are ‘antagonistic pleiotropy’, its offshoot, ‘the disposable soma’, and the ‘grandmother effect’.

Antagonistic pleiotropy offers the concept of trade-off whereby genes that are advantageous, bolstering fitness during the reproductive period, become disadvantageous thereafter, causing biological breakdown (diminished fitness), characterized in humans as aging-related diseases (26,27). The disposable soma adds an additional dimension to this thesis by suggesting another trade-off, i.e., energy investment in reproduction at the expense of somatic fitness or vice versa (28). The grandmother effect rests on the proposition that the investment of post-reproductive women in the fitness of their offspring enhances the survival of their grownup offspring and grandchildren (29,30). While antagonistic pleiotropy and the disposable soma regard the post-reproductive period as non-adaptive, the grandmother effect regards the post-reproductive period as adaptive in that it offers selective advantage by channeling energy into the sustaining of descendents (31).

All three hypotheses view the pre-and post-reproductive periods as intrinsically connected in a causal relationship. Antagonistic pleiotropy and the disposable soma propose that the reproductive period is a major determinant of the post-reproductive period. In contrast, the grandmother effect suggests the other way around. Yet another alternative exists, that is, the duration of the post-reproductive period is fashioned by stochastic events so that aging is simply a random add-on of a variable time span to the reproductive period (32).

Reproduction, Longevity and CVD in Women

Women with late menopause live longer than do their peers (33). The same holds for women who bear children later in life (34,35). What is more, late menopause is associated with diminished susceptibility to CVD (33,³⁶,37). Thus, delayed menopause denotes better somatic fitness, which entails not only increased longevity but also being alive longer to care for children and grandchildren, a concept in line with both the add-on and the grandmother effect models of aging. Other research suggests that women with fewer children live longer (38, but see 39), a finding that supports the disposable soma model of aging.

Studies that tested the ‘fetal origin’ hypothesis have provided an additional appraisal of somatic fitness in women. These studies have focused on the intrauterine environment and the early postnatal growth as major factors that shape the offspring’s somatic fitness (40–43). The central theme guiding the fetal origin hypothesis is this: Due to their unfavorable intra-uterine environment, small for gestational age (SGA) and premature babies are susceptible to aging-

related diseases, CVD in particular, during adulthood. However, recent investigations have found that maternal genetic determinants account in part for the predilection of SGA and premature newborns to CVD in adulthood. Women who had experienced pregnancy complicated by spontaneous abortion, pre-eclampsia, or the birth of SGA or premature babies were themselves prone to CVD later in life (44–46).

Collectively, these studies suggest that while late menopause is a signature of better somatic fitness, pre-eclampsia and giving birth to SGA or premature babies reflect diminished somatic fitness.

Conclusions

One unambiguous message emerges as we figure our way through the maze of expression of CVD in modern societies. CVD are not just diseases of aging. They are phenotypes of somatic fitness and therefore aging itself. The gender gap in human longevity possibly results from the superior ability of women to contain the harmful effects of oxidative stress and perhaps inflammation through estrogen and somatic cell selection. The evolutionary forces that have ultimately defined the life span of women are displayed in the factors that fashion the pre and post menopausal periods. We might debate endlessly the specific causes of CVD and the sexual dimorphism in their expressions. But in the final analysis, a far better understanding of the causes of CVD will emerge when we gain insight what aging is all about.

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