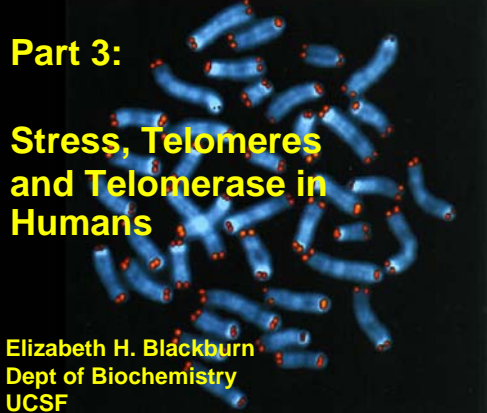


**Part 3:**

**Stress, Telomeres and Telomerase in Humans**

Elizabeth H. Blackburn  
Dept of Biochemistry  
UCSF



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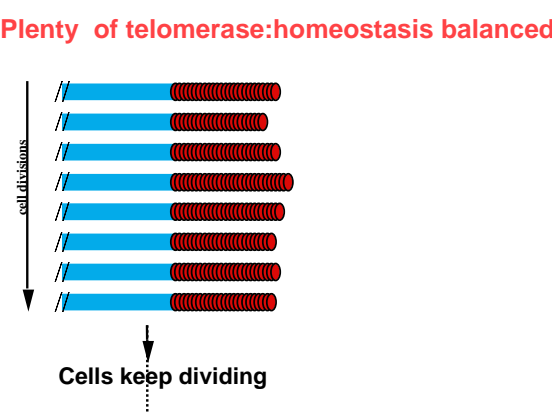
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**Plenty of telomerase: homeostasis balanced**



cell divisions

Cells keep dividing

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How do we age?

A multi-faceted process?

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How do we age?

A multi-faceted process?

- increased susceptibility to diseases

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How do we age?

A multi-faceted process?

- increased susceptibility to diseases
- how much is
  - environment/life factors?
  - genetic?

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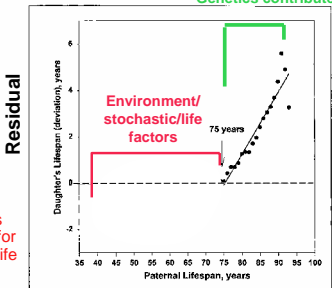
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Genetics contributes a lot

Environment/stochastic/life factors

75 years

zero expected if inheritance is unimportant for determining life span

increasing with parental life span expected if life span is inherited

Residual: the difference between each daughter's life span and the cohort mean life span

Gavrilova NS and Gavrilova LA. (2001) Journal Anti-Aging Med.

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- Elderly subjects demonstrating **exceptional longevity** have generally been spared major age-related diseases, such as **cardiovascular disease (CVD)**, **diabetes mellitus and cancer**, which are diseases that are responsible for **most** deaths in the elderly.

*Atzmon et al Journal of the American Geriatrics Society, 2004. Vol. 52, 274*

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**Cardiovascular disease, diabetes and cancer**

*Atzmon et al Journal of the American Geriatrics Society, 2004. Vol. 52, 274*

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cell divisions

Telomeres replenished by telomerase

Cells keep dividing

- Active: stem cells, germ cells  
- Detectable: many normal adult cell types (regulated activity)  
- Highly active: ~90% of human tumors

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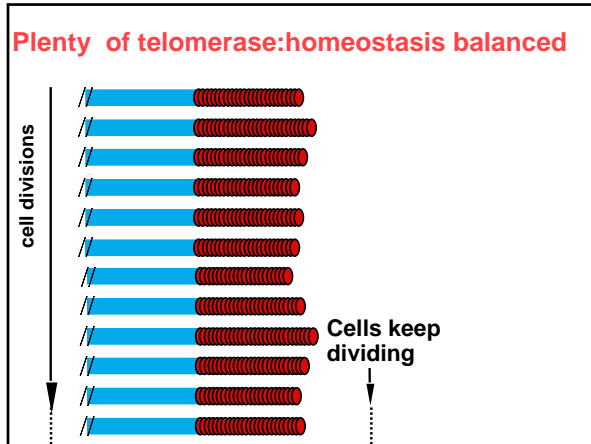
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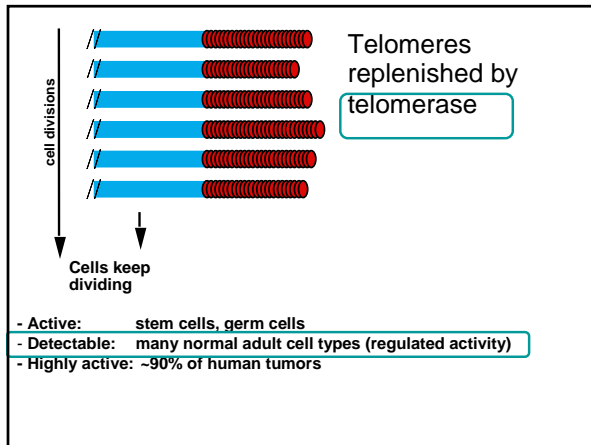
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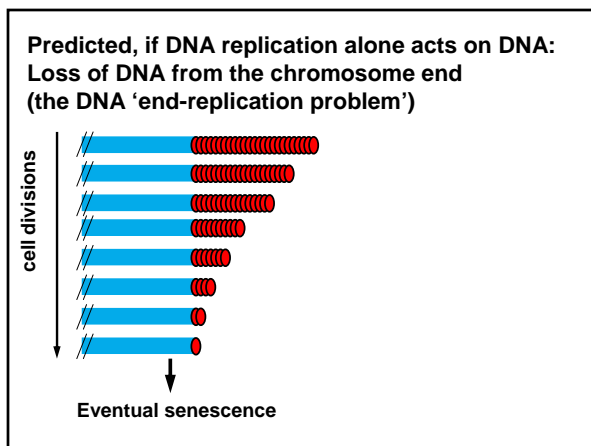
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Predicted, if **some** telomerase:  
**Slower loss** of DNA from the chromosome end

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Predicted, if **less** telomerase:  
**Faster loss** of DNA from the chromosome end

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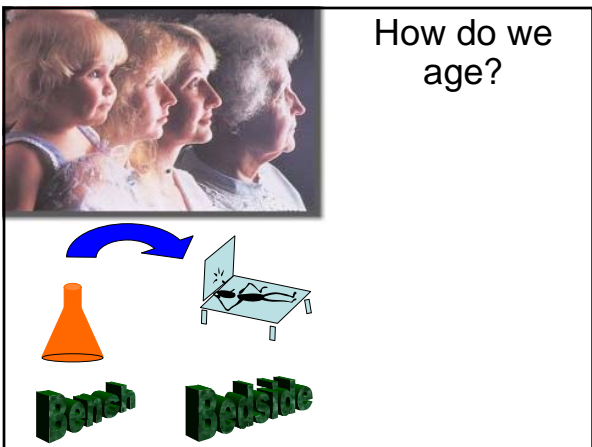
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How do we age?



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How do we age?

Bench Bedside

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One mutated hTER gene copy  
\* Affected family members

Vulliamy et al, Nature, 2001

One wild type gene copy

A rare inherited condition in humans:  
(called dyskeratosis congenita)  
Premature death from progressive bone marrow failure\*  
when one gene copy of telomerase RNA is deficient

\*death in early adulthood to middle age  
- shorter telomeres  
- immune system becomes exhausted  
- cancer-prone

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A full human lifespan requires **both** telomerase RNA alleles to be functional:  
Telomerase gene product **quantity** matters

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**Effects *in vivo* of common variations in telomere maintenance in humans?**

Reported: people aged 60 years or older with **shorter** blood cell telomeres have **higher mortality rates**

- Shorter** telomeres associate with:
- 3.2 fold **higher mortality** rate from heart disease
  - 8.5 fold **higher mortality** rate from infectious disease
  - poorer survival** overall from aggregate of all causes

*Cawthon et al, Lancet 361: 393-395, 2003*

**What came first?**

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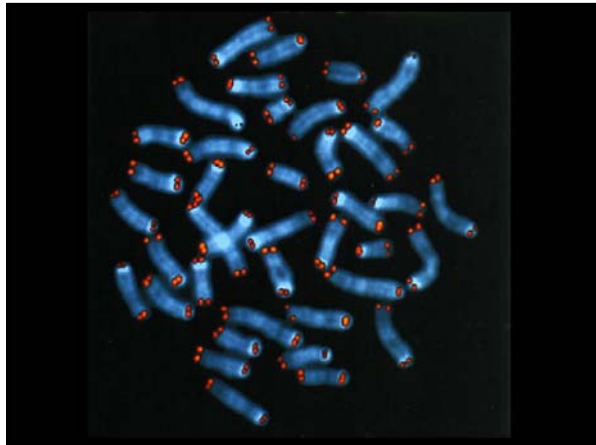
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**STUDY DESIGN**

**Psychological stress:**  
62 healthy premenopausal women (aged 20-50 )  
biological mothers of  
a healthy child (control mothers)  
a chronically ill child (caregiving mothers).

All completed a standardized 10-item questionnaire assessing level of perceived stress over the past month.  
high score => high perceived stress level

**Other parameters also measured**

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**Psychological Stress, Risks of Cardiovascular Disease and Telomeres/Telomerase/Oxidative Stress**

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**Psychological Stress, Risks of Cardiovascular Disease and Telomeres/Telomerase/Oxidative Stress**

**Three Markers of Cellular Aging**

- Telomerase activity
- Telomere length
- Cellular Oxidative stress

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**Caregiver mothers and chronic stress**

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**Other parameters were also measured**

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**Caregiver mothers and chronic stress**

**Questions**

Are

- level of perceived stress (both groups)
- duration of caregiving (caregiver group) related to markers of cell aging?

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**Caregiver mothers and chronic stress**

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Are

- level of perceived stress (both groups)
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**Three Markers of Cellular Aging**

- Telomerase activity
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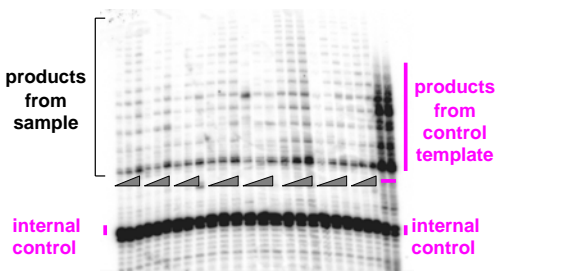
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**Caregiver mothers and chronic stress**

**Telomerase Activity Assay (TRAP)**



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**Caregiver mothers and chronic stress**

How cellular oxidative stress was measured:

- the ratio of isoprostanes per mg creatinine / Vitamin E. represents net oxidative stress effect

(one marker of oxidative stress and one marker of antioxidant defenses)

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**Caregiver mothers and chronic stress**

Perceived stress (all across the whole sample) was associated with shorter telomeres, lower telomerase activity and higher oxidative stress

	Perceived stress
Telomere length	-.31** n = 54
Telomerase activity	-.24* n=59
Oxidative stress index	.27* *n=54

Epel et al, 2004, PNAS \*\*: p < 0.01, \*:P < 0.05

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**Caregiver mothers and chronic stress**

Perceived stress (all across the whole sample) was associated with shorter telomeres, lower telomerase activity and higher oxidative stress - as was years of caregiving

	Perceived stress	Years of caregiving
Telomere length	-.31** n = 54	-.40 ** n = 36
Telomerase activity	-.24* n=59	-.35 * *n = 37
Oxidative stress index	.27* *n=54	.33 * *n = 30

Epel et al, 2004, PNAS \*\*: p < 0.01, \*:P < 0.05

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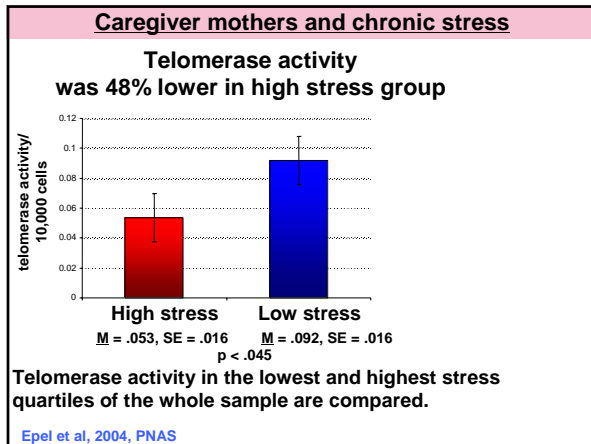
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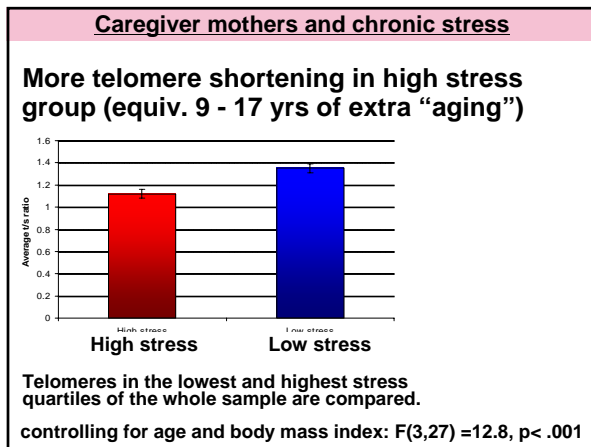
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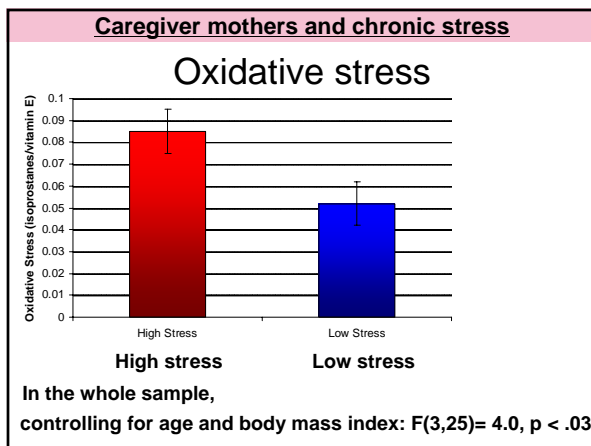
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**Caregiver mothers and chronic stress**

Summary

- Stress perception & caregiving duration are linked to cell aging markers
  - Telomerase
  - Telomere length
  - Oxidative stress
- Causal direction?
- Possible mechanisms?

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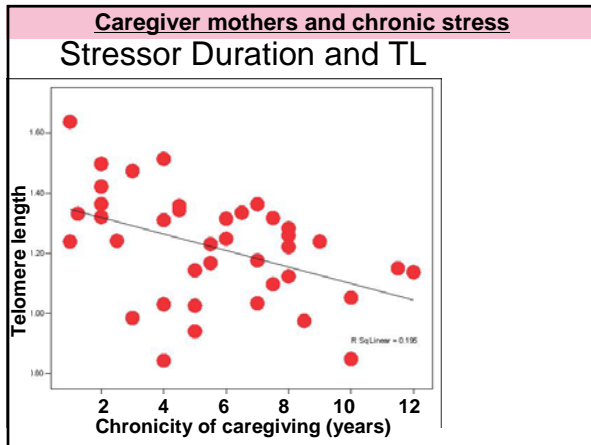
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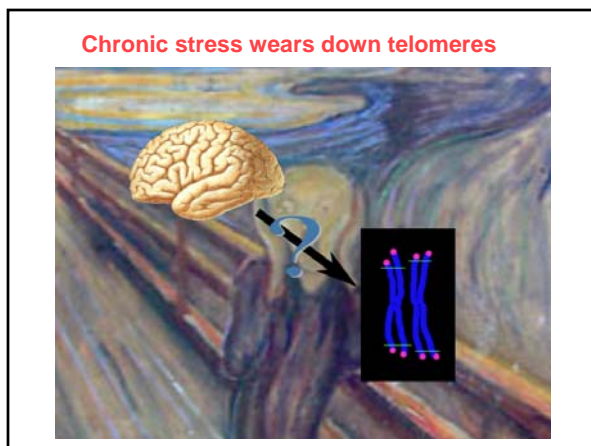
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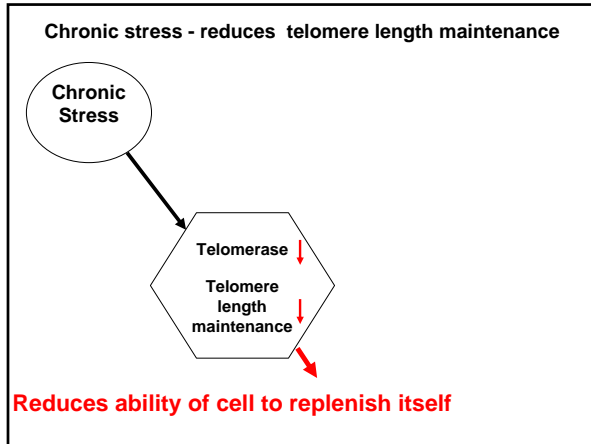
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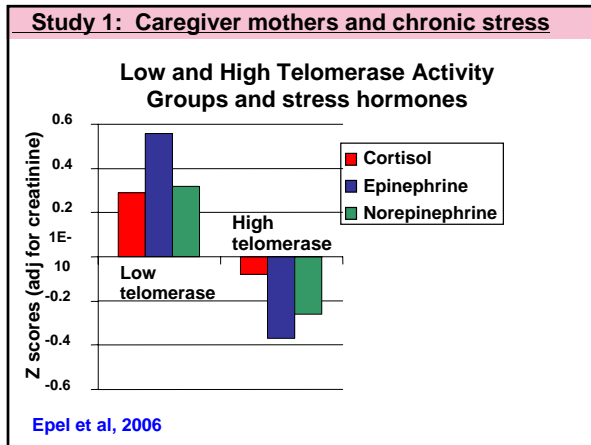
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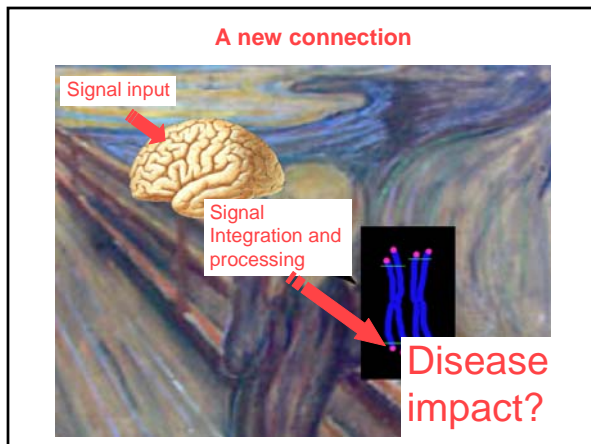
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**Telomere maintenance and risk of cardiovascular disease**  
**A link in vivo**



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**Telomere maintenance and risk of cardiovascular disease**  
**A link in vivo**



In the largest epidemiological study of risk factors for cardiovascular disease, six prominent factors were shown to be:

- smoking
- poor lipid profile
- high blood pressure
- diabetes
- abdominal obesity
- psychological stress

(Yusef et al, Lancet 2004:304).

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- diabetes
- abdominal obesity
- psychological stress

(Yusef et al, Lancet 2004:304).

\*Chronic stress was associated with three markers of cellular aging:

- Lower telomerase activity
- Higher oxidative index
- Shorter telomere length

\*Epel et al, 2004

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**Telomere maintenance and risk of cardiovascular disease**  
**A link in vivo**

In the largest epidemiological study of risk factors for cardiovascular disease, six prominent factors were shown to be:

- smoking
- poor lipid profile
- high blood pressure
- diabetes
- abdominal obesity
- psychological stress

(Yusef et al, Lancet 2004:304).

- smoking
- cholesterol/blood lipids
- resting cardiovascular activity
- fasting glucose
- adiposity
- psychological stress

Stress was associated with three markers of cellular aging:

- Lower telomerase activity \*
- Higher oxidative index
- Telomere length

\*Epel et al, 2006

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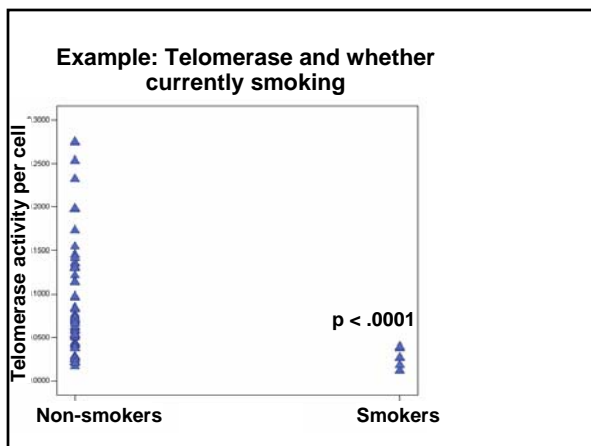
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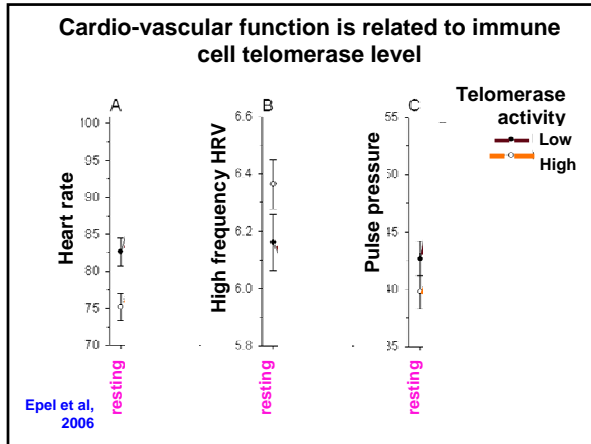
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**Telomere maintenance and risk of cardiovascular disease**  
**A link in vivo**

- We have found\*: the first evidence in vivo that **low telomerase alone**, even in the absence of obvious telomere shortening, is **associated** with 6 major risk factors (including chronic psychological stress) for cardiovascular disease in people

Is telomerase status in normal cells in people an indicator of disease risk?

\*Epel et al. 2006

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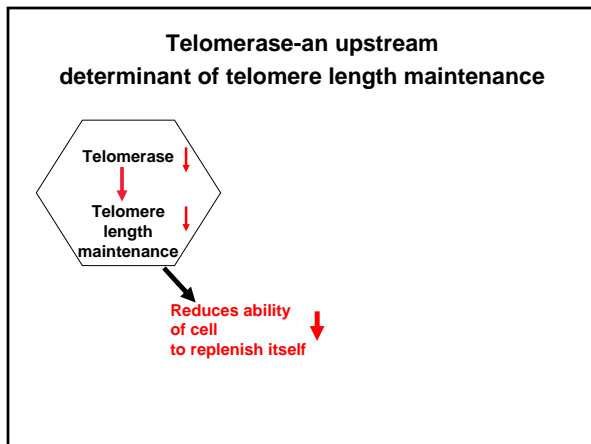
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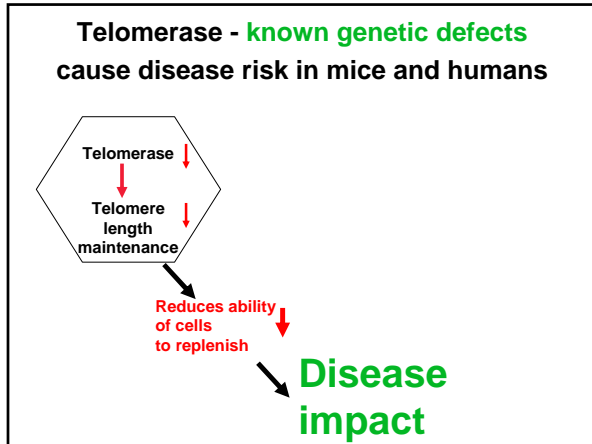
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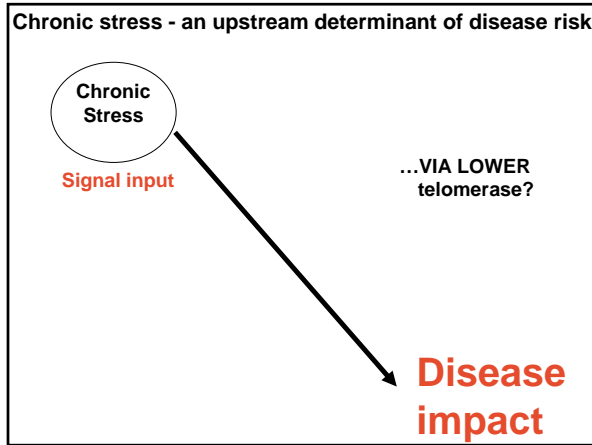
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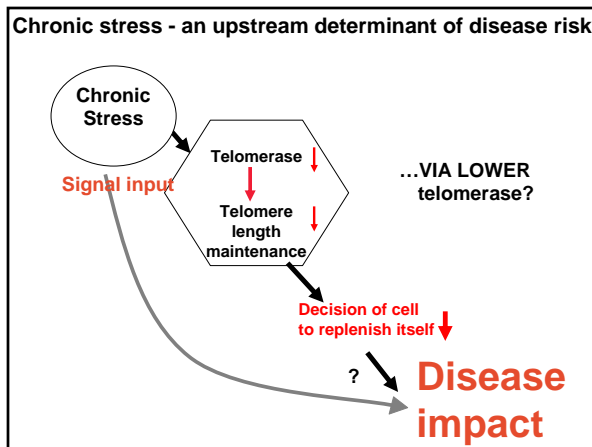
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Low telomere length linkage to very common disease states	
<b>Cancer</b>	Vulliamy, T. et al. (2001) Joshua et al., Shen et al (2007)
<b>Cardiovascular disease</b> (plaques, heart attacks, calcific aortic valve stenosis)	Brouillette, S. et al. (2003) Benetos, A. et al. (2004) Kurz, D. J. et al. (2006) Starr et al (2007) Brouillette et al (2007)
<b>Vascular dementia</b>	von Zglinicki, T. et al. (2000)
<b>Degenerative conditions</b> (osteoarthritis, osteoporosis)	Zhai, G., et al. (2006) Valdes, A. M. et al. (2007)
<b>Diabetes</b>	Valdes, A. M. et al. (2005) Aviv, A. et al. (2006)
<b>General risk factors for chronic disease</b> - obesity and insulin resistance	Gardner, J. P. et al. (2005)

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**cardiovascular disease, diabetes and cancer**  
the elderly.

*Atzmon et al Journal of the American Geriatrics Society, 2004. Vol. 52, 274*

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How do we age?

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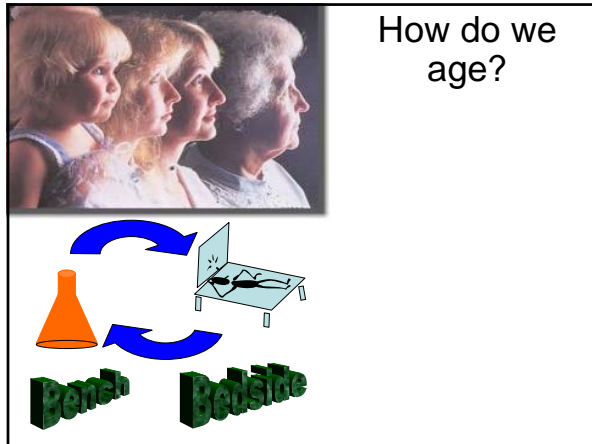
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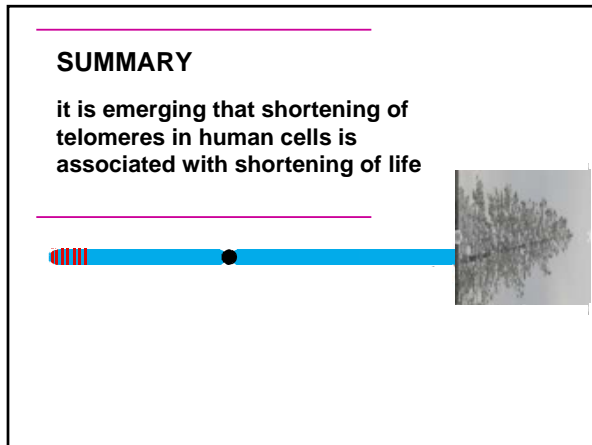
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