Breast Cancer and Senescence

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Risk Factors

- Female
- Family History
- Age
- Age at 1st period
- Age at menopause
- Age at 1st pregnancy
- Nulliparity
- History of benign breast disease
- Obesity
- HRT

Genetic Factors

- Oncogenes
- Tumor suppressor genes
- DNA repair genes
- Carcinogen activating/deactivating genes
- Cell cycle genes
- Cell cycle checkpoint genes
- Cell death genes
- Cell signaling genes
- Cellular senescence genes
- Cellular differentiation genes
- Metastasis/invasion genes

Jeanne Calment

21 February 1875- 4 Agustus 1997

Senescence

- Proliferation capacity in cell culture
  - Phase 1: little proliferation before 1st passage
  - Phase 2: rapid cell proliferation
  - Phase 3: gradual grind to a complete halt
- Hayflick (1965) → "Hayflick limit" : expression of aging or senescene at the cellular level
- *Stable and long term-loss of proliferative capacity despite continued viability and metabolic activity*

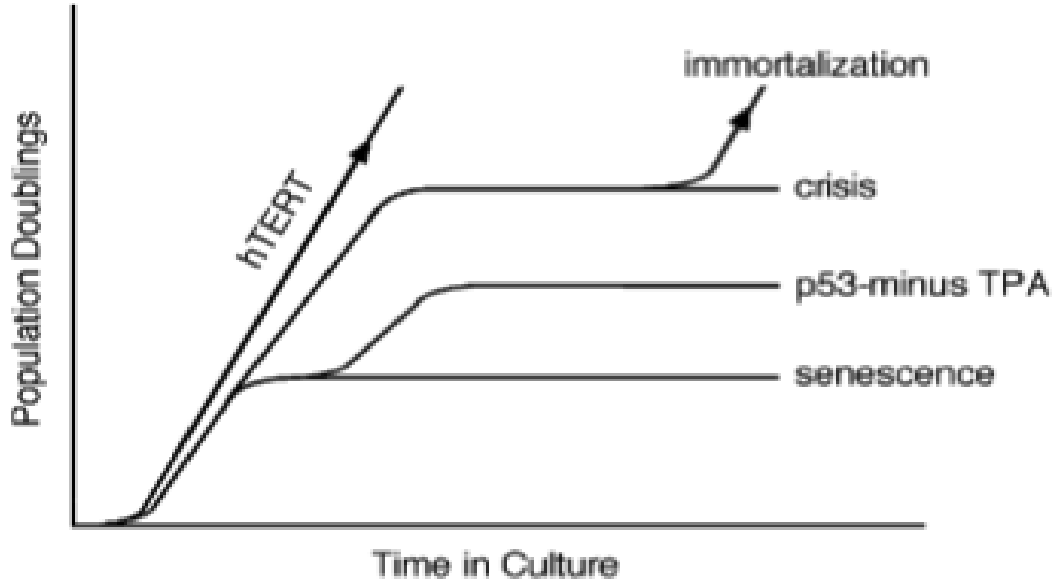


Fig. 4. Terminal proliferation arrest (TPA) states. Normal cells divide a limited number of times before permanently exiting the cell cycle and remaining in a viable non-proliferative state referred to as senescence (1). If p53 is inactivated in these cells, the cells may resume dividing a limited number of times, before they permanently exit the cell cycle (p53-minus TPA) (38,39). If p53 and the pRb/p16^{INK4a} pathway are both disrupted, for example, by the presence of SV40 or HPV viral oncoproteins, the cells may bypass senescence but subsequently arrest in a state referred to as crisis (44). A rare cell (~1 in 10^7) may escape from crisis and become immortalized. Transduction of some normal cells with hTERT expression constructs may result in expression of telomerase and bypass of senescence.

(Reddell 2000)

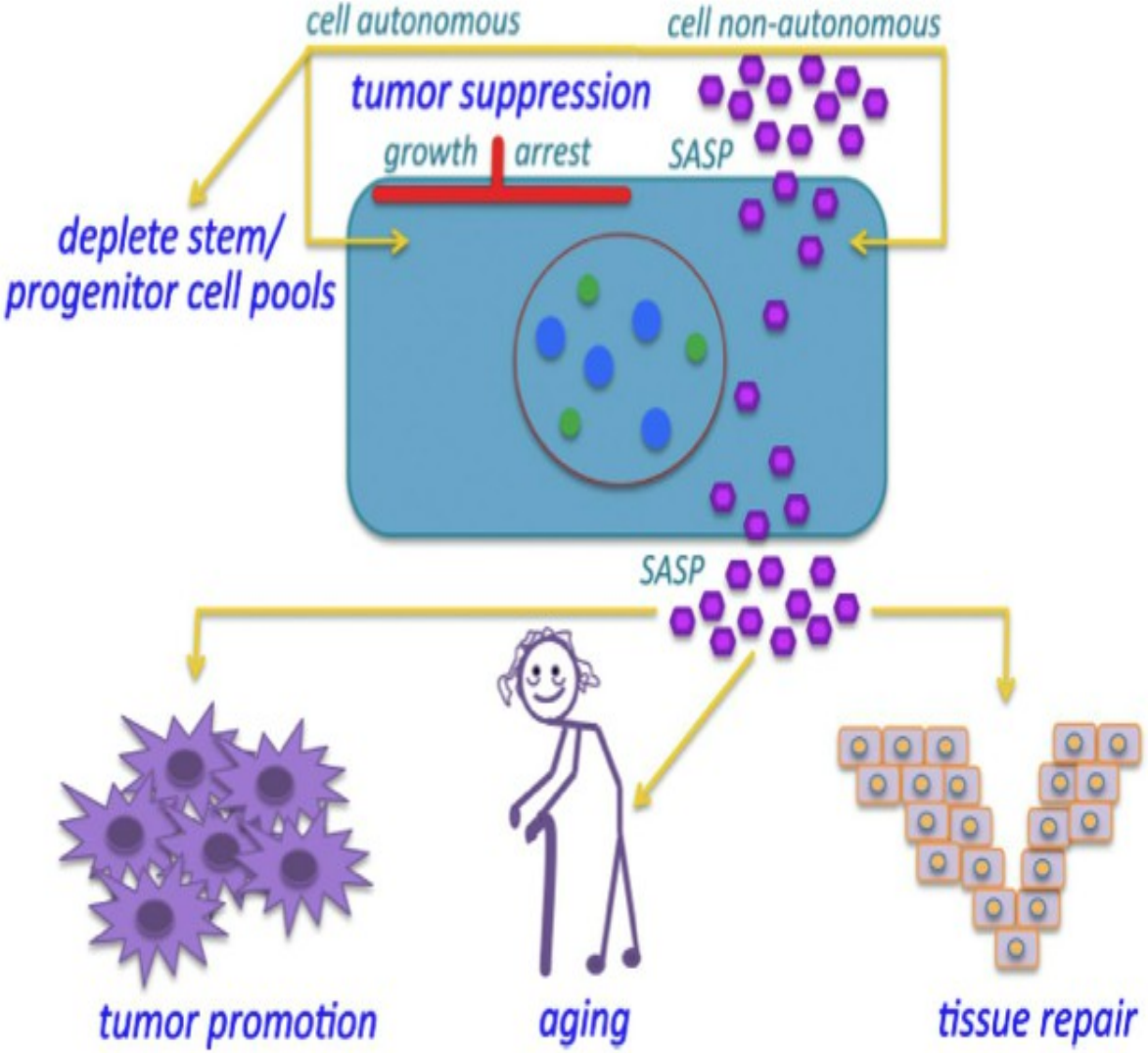
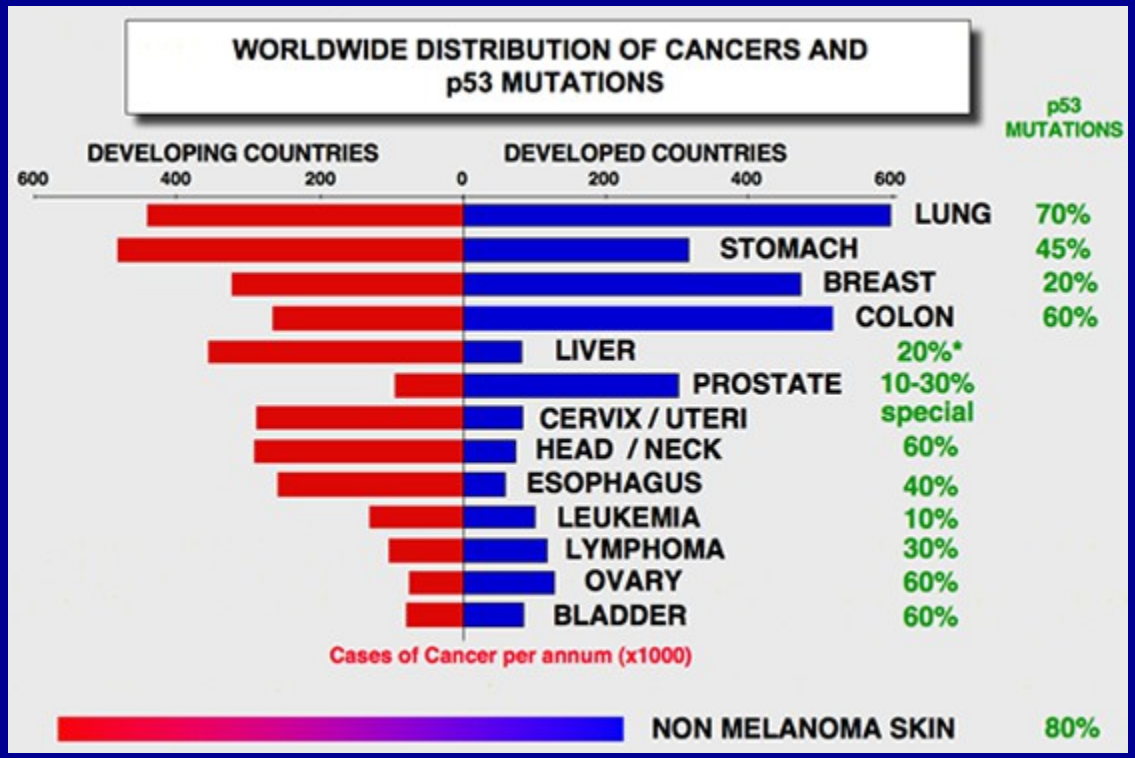
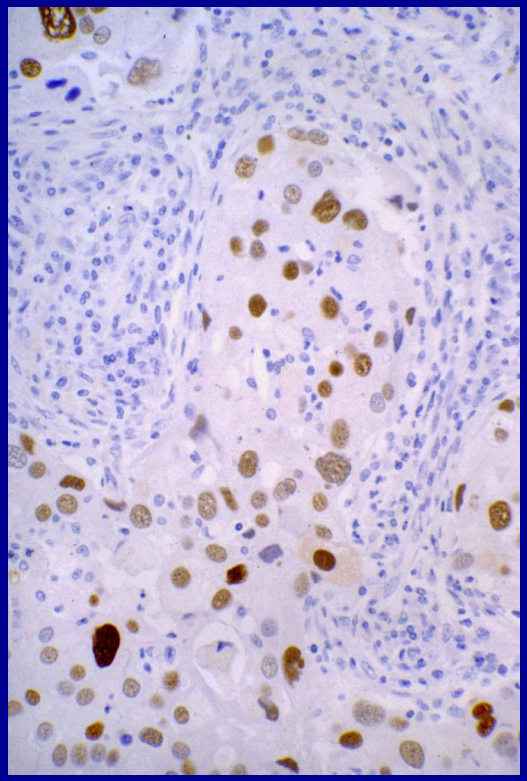


Figure 2. **Biological activities of cellular senescence.** Senescent cells arrest growth owing to cell autonomous mechanisms, imposed by the p53 and p16INK4a/pRB tumor suppressor pathways, and cell nonautonomous mechanisms, imposed by some of the proteins that comprise the SASP. The growth arrest is the main feature by which cellular senescence suppresses malignant tumorigenesis but can contribute to the depletion of proliferative (stem/progenitor) cell pools. Additionally, components of the SASP can promote tumor progression, facilitate wound healing, and, possibly, contribute to aging.

(Rodier, Campisi 2011)

p53 mutation in cancer

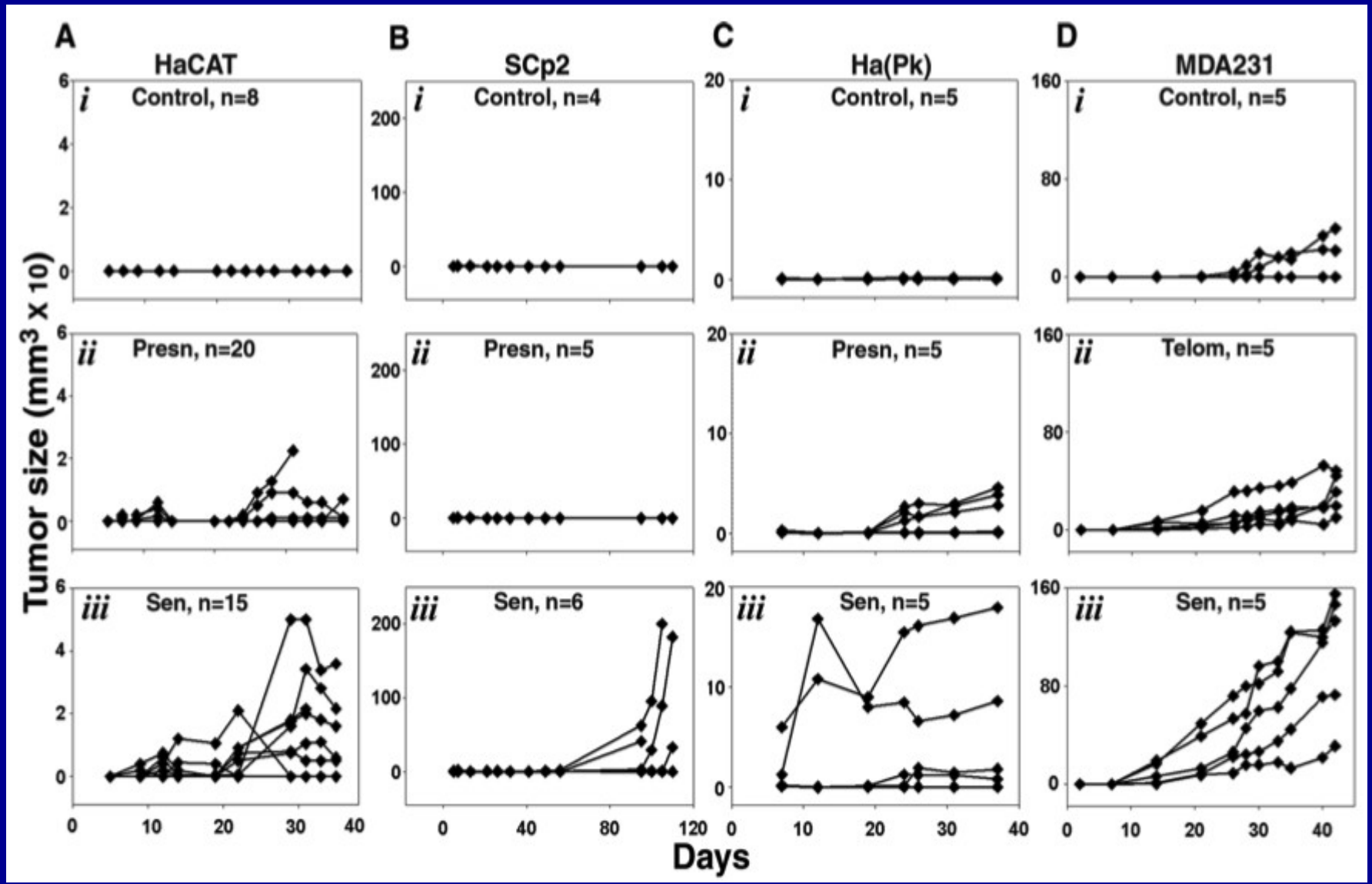




~50% of all cancer patients involve p53 mutation

Breast cancer: senescence

- Immortalization is an essential step in the malignant transformation of normal cells (?)
- Senescence is the barrier against tumorigenesis (?)
- Senescent stromal cells may actually promote the proliferation and tumorigenesis of mutant epithelial cells

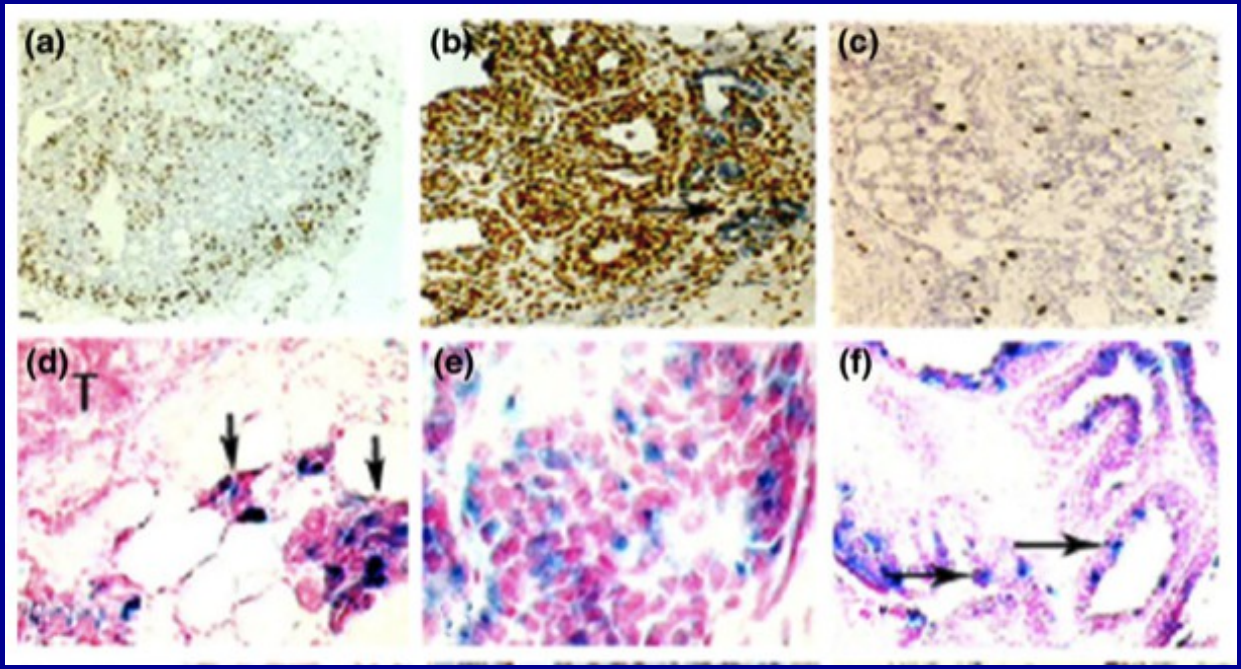


(Kretolica et al 2001)

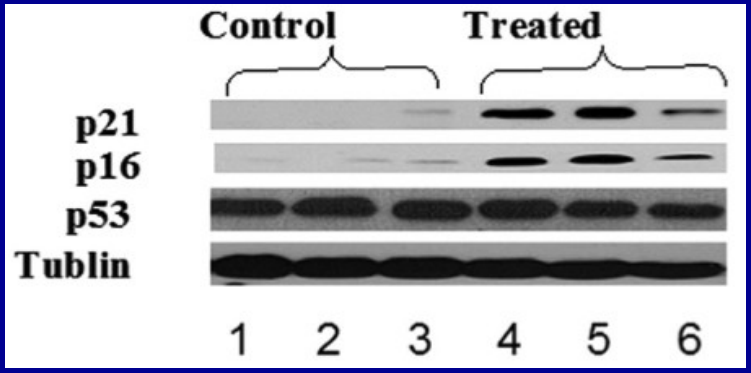
DHEA

- Precursor of testosterone and 17 Beta-estradiol
- High level DHEA: less breast carcinoma (premenopause) more breast ca (postmenopause)
- Non hormonal-dependent

DHEA



(Shilkaitis et al 2005)



Li Fraumeni syndrome

- Rare autosomal hereditary cancer syndrome
- Telomere dysfunction, spontaneous immortalisation, genomic instability
- Breast cancer in 50% of LFS carrier