Aging and Cancer

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World record times for marathon (female)

Time (minutes) vs. Age (years)

Raw data from Association of Road Racing Statisticians
http://www.arrs.net/SA_Mara.htm
“Cancer and Aging... here, two different manifestations of the same process... accumulation of UV damage.”
Cancer Characteristics:
1. Uncontrolled cell division
Age-associated diseases

- Osteoporosis
- Alzheimer's Disease
- COPD
- Parkinson's Disease
- Cardiovascular Diseases
- Diabetes
- Arthritis
- Cerebrovascular Disease (stroke)
- Pulmonary Fibrosis
- Chronic Liver Disease
- Sarcopenia
- Anemia

- Cancer
Incidence of pancreatic cancer in New South Wales

A woman’s risk of developing pancreatic cancer increases exponentially after menopause may be linked to a decrease in estrogen. Men do not show this increase in later ages.
Cancer characteristics:
2. Cancer rates increase with age

Why?
Aging and cancer

Lifetime risk of developing cancer: \textbf{1 in 3}

Lifetime risk of dying from cancer: \textbf{1 in 5}

1.7 million new cases, 0.6 million deaths in the U.S. (2017)

- 77\% > age 55
- 53\% > age 65

(2013 SEER data)

\textbf{Age is the most potent risk factor known for cancer}
### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>161,360</td>
<td>252,710</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,990</td>
<td>105,510</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>71,420</td>
<td>64,010</td>
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<tr>
<td>Urinary bladder</td>
<td>60,490</td>
<td>61,380</td>
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<tr>
<td>Melanoma of the skin</td>
<td>52,170</td>
<td>42,470</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,610</td>
<td>34,540</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>40,080</td>
<td>32,100</td>
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<tr>
<td>Leukemia</td>
<td>36,290</td>
<td>26,840</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>35,720</td>
<td>25,700</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>29,200</td>
<td>23,380</td>
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<tr>
<td><strong>All Sites</strong></td>
<td><strong>856,150</strong></td>
<td><strong>852,630</strong></td>
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### Estimated Deaths

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<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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<td>Lung &amp; bronchus</td>
<td>64,590</td>
<td>71,280</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>27,150</td>
<td>40,610</td>
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<tr>
<td>Prostate</td>
<td>26,730</td>
<td>23,110</td>
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<tr>
<td>Pancreas</td>
<td>22,300</td>
<td>20,750</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>19,610</td>
<td>14,080</td>
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<tr>
<td>Leukemia</td>
<td>14,300</td>
<td>10,520</td>
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<tr>
<td>Esophagus</td>
<td>12,720</td>
<td>10,200</td>
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<tr>
<td>Urinary bladder</td>
<td>12,240</td>
<td>9,310</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,450</td>
<td>8,690</td>
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<tr>
<td>Brain &amp; other nervous system</td>
<td>9,620</td>
<td>7,080</td>
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<tr>
<td><strong>All Sites</strong></td>
<td><strong>318,420</strong></td>
<td><strong>282,500</strong></td>
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Cancer characteristics:
3. Adult Cancer Spectrum

"WHY?"

Childhood cancer shows inverse of this
Epithelial Tissues
-typically actively dividing

Some examples

Others:
- Oral cavity
- Lungs
- Breast
- Liver
- Kidney
- Colon/Rectum
- Cervix
- Uterus
- Ovary
- Prostate
The hallmarks of cancer

- Hanahan & Weingberg, CELL 2011
Tumorigenesis

• Multiple barriers limit tumor development therefore multiple mutations must accrue

• Multiple rounds of selection (Tomlinson)

• Mutator phenotype (L. Loeb)

![Diagram](image-url)

80 divisions
Cancer characteristic:
4. Mutations

Somatic mutation in cancer and normal cells. Science Sept. 2015
Possible sources of mutation

1. Radiation
2. Carcinogen exposure (e.g. dietary, smoking)
3. Reactive oxygen species (mitochondria)
4. Inflammation
5. Cell proliferation
   - DNA replication errors
   - Chromosomal damage/instability
Cancer characteristic:
5. Epigenetic changes
EPIGENETICS

A mechanism for regulating gene activity independent of DNA sequence that determines which genes are turned on or off:
- in a particular cell type
- in different disease states
- in response to a physiological stimulus

Genes are turned on and off by modifications to the tails of histones, such as acetylation.

Source: https://pinkhope.org.au/what-is-epigenetics/
Association of DNA with histones showing some common posttranslational modifications that influence this interaction.

Source: http://www.wiringthebrain.com/2013/01/the-trouble-with-epigenetics-part-1.html
Cancer Characteristic:
6. Chromosomal Instability (CIN)
Nothing in biology makes sense

Theodosius Dobzhansky (1900-1975)
• "Immortality"
• Divide & conquer!
• Limited by carrying capacity

Unicellular

→ evolved to

Multicellular

• "Mortal"
• Specialization/co-operation
• (germ line, somatic; stem)
• Homeostasis/Self-limiting

CC

CANCER
Uncontrolled cell division is at the heart of the cancer problem
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**Weight of the Earth**

**Number of particles in known universe!**
Normal human cells have limited cell division potential
Normal cells’ limited division potential

"Hayflick Limit" (replicative senescence)

Prevent st clonal overgrowth

Cell yield during aging in a human diploid cell culture.


Tumor suppressors
• P53
• pRB
Stem cell divisions & cancer risk

Cell division is risky!

Tomaseti and Vogelstein, Science Jan. 2015
**Replicative Senescence** – a permanent block to a cell’s ability to proliferate

(Apoptosis too)
SENESCENCE

ONCOGENE

APOPTOSIS

TUMOR SUPPRESSOR
Antagonistic Pleiotropy

Beneficial early in life but detrimental later in life
Limited somatic cell replication

(A serious threat in large, long-lived organisms)

Aging

Cancer!
"C’mom, c’mom—it’s either one or the other."
Cellular Senescence

Several initiating triggers:

- DNA damage
- Radiation
- Activated oncogenes (oncogene induced senescence)
- Oxidative stress (stress induced senescence)
- Excess cell division (replicative senescence)

Common theme - all potentially oncogenic!

Implies a counting mechanism: a “mitotic clock”
Human telomeres

1000 – 2000 Repeats (6-12 Kbp)

200 – 600 nuc

TTAGGG

TTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGG

AATCCCAATCCCAATCCCAATCCCAATCCCAATCCCAATCCCAATCCCAATCC
6 protein “Shelterin” complex
Telomeres shorten with each division due to the end-replication problem.
Telomeres shorten with each division due to the end-replication problem.
Telomeres shorten with each division due to the end-replication problem.
Telomeres shorten with each division due to the end-replication problem
Cell division

DNA damage (e.g. oxidative stress)
Telomeres gradually shorten with age

Telomere lengths measured in Peripheral Blood Leukocytes (PBL)

$Y = 7.37 - 0.022X$
$r = -0.41, P < 0.0001$
“The terminus is the heel of Achilles of the DNA double helix...”

--A. Olovnikov, J. Theoretical Biology (1973)
S.E. Artandi, New England Journal of Medicine, Sep 21 2006, 1195-1197
Normal cells have a **limited division potential**

![Graph showing cell yield during aging in a human diploid cell culture.](image)

- **Hayflick Limit** (replicative senescence)

Replicative Senescence
– permanent block cell proliferation
– prevents chromosomal instability due to extreme telomere shortening
DNA Repair (NHEJ) at dysfunctional telomeres
“Breakage-Fusion-Bridge cycles”
_Barbara McClintock (1930s)
Cancer cells with short telomeres exhibit anaphase bridges

Parental cells
normal anaphase

Elevated frequency of anaphase bridges in cells w/ short telomeres
Telomeres in human prostate cancer

Normal

stroma

Short telomeres

Tumor
Anaphase bridging
(Colon)
“IEN”
Intra-epithelial neoplasia

Why takes so long??

<table>
<thead>
<tr>
<th>Location</th>
<th>Normal Risk</th>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
<th>Tertiary Prevention</th>
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<tbody>
<tr>
<td>Colon</td>
<td>5–20 yrs</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Head and neck</td>
<td>4–10 yrs (tobacco use)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>-</td>
<td>Prevention of IEN</td>
<td>Prevention of IEN</td>
<td>Prevention of cancer</td>
</tr>
<tr>
<td>Cervix</td>
<td>-</td>
<td>Prevention of IEN</td>
<td>Prevention of IEN</td>
<td>Prevention of cancer</td>
</tr>
<tr>
<td>Lung (smokers)</td>
<td>20–40 pack yrs*</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Skin (non-melanoma)</td>
<td>30–60 yrs</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Breast</td>
<td>20 yrs</td>
<td>Atypical hyperplasia</td>
<td>Severe dysplasia</td>
<td>Adjuvant therapy, treatment of IEN, Prevention of cancer</td>
</tr>
<tr>
<td>Prostate</td>
<td>20 yrs</td>
<td>PIN</td>
<td>TIS</td>
<td>-</td>
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<tr>
<td>Bladder</td>
<td>20 yrs</td>
<td></td>
<td></td>
<td>-</td>
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Normal Prostate

Basal cells

Luminal cells
Pre-cancerous prostate lesion (PIN)
Human fibroblasts early in vitro culture
Human fibroblasts
Long-term in vitro culture

SA-beta galactosidase
Senescent cells

Characteristics

- Programmed response to variety of stresses
- Non-proliferative, Growth-arrested
- Resistant to apoptosis
- Changes in gene expression programs
  - Senescence-Associated Secretory Phenotype (SASP)
- Increase with age
- Present at sites of age-related pathologies
Senescent cells

Purpose? (why was this mechanism selected for?)

- Anti-cancer (prevents clonal expansion/proliferation)
- Roles in embryonic development
- Anti-viral? (cGAS-STING can initiate SEN)
- Encourages tissue repair/wound healing
  - Transient wave in youth
    - But chronic presence is problematic
    - In cancer – “wound that doesn’t heal”
SENESCENT CELLS – altered behavior

Senescence-associated secretory phenotype (SASP)

Produce and secrete:
- Pro-inflammatory cytokines
- Growth and survival factors
- Angiogenic factors
- Matrix-degrading proteases
Inflammation is a risk factor for cancer

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Cancer</th>
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<tbody>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>Colorectal cancer</td>
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<tr>
<td>Bronchitis</td>
<td>Lung cancer</td>
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<tr>
<td>Gastritis</td>
<td>Stomach cancer</td>
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<tr>
<td>Hepatitis</td>
<td>Liver cancer</td>
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<td>Cholecystitis</td>
<td>Gall bladder cancer</td>
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<td>Pancreatitis</td>
<td>Pancreatic cancer</td>
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<tr>
<td>Sunburn</td>
<td>Skin cancer</td>
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<tr>
<td>Schistosomiasis</td>
<td>Bladder cancer</td>
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<tr>
<td>Esophagitis</td>
<td>Esophageal cancer</td>
</tr>
</tbody>
</table>
Senescent cells and the aged microenvironment may promote:

- Cancer risk
- Cancer progression/Chemo resistance/Metastasis

Also, cancer treatments can induce senescent cells
Aged tumor microenvironment promotes tumors and metastases

Bianchi-Frias et al., Mol Cancer Res. 2019
Jan;17(1):321-331
The aged microenvironment facilitates distant melanoma metastasis.

Kerrie L. Marie, and Glenn Merlino Cancer Discov
2013;9:19-21
Senescent cells

Antagonistic pleiotropy

- Anti-cancer
- Embryonic dev.
- Anti-viral(?)
- Tissue repair (transient)

- Resist Apoptosis/Accumulate
- SASP
- Pro-inflammatory
- Pro-cancer

Youth

Age
Naturally occurring p16<sup>Ink4a</sup>-positive cells shorten healthy lifespan

Darren I. Baker<sup>1</sup>, Benoist G. Chiche<sup>2</sup>, Marj Durik<sup>3</sup>, Melinda F. Wijher<sup>4</sup>, Cynthia L. Brown<sup>5</sup>, Jian Zhang<sup>6</sup>, Rachel A. Saito<sup>7</sup>, Karluk R. Jagielski<sup>8</sup>, Grace Cawaeling Verossa<sup>9</sup>, Abdulla Hammoud<sup>10</sup>, Khadijah A. Kharela<sup>11</sup>, Jordan D. Miller<sup>2</sup> & Jan M. van Deursen<sup>1</sup>

Cellular senescence, a stress-induced irreversible growth arrest often characterized by expression of p16<sup>Ink4a</sup> (encoded by the Ink4a/Aip locus, also known as Cdkn2a) and a distinctive secretory phenotype, prevents the proliferation of preneoplastic cells and has beneficial roles in tissue remodeling during embryogenesis and wound healing. Senescent cells accumulate in various tissues and organs over time, and have been speculated to have a role in aging. To explore the physiological relevance and consequences of naturally occurring senescent cells, here we use a previously established transgenic, INK-ATTAC, to induce apoptosis in p16<sup>Ink4a</sup>-expressing cells of wild-type mice by injection of APO1877 twice a week starting at one year of age. We show that compared to vehicle alone, APO1877 treatment extended median lifespan in both male and female mice of two distinct genetic backgrounds. The clearance of p16<sup>Ink4a</sup>-positive cells delayed host-mediated and attenuated age-related deterioration of several organs without apparent side effects, including kidney, heart and fat, where clearance preserved the functionality of glomeruli, cardiac protective K<sub>ATP</sub> channels and adipocytes, respectively. Thus, p16<sup>Ink4a</sup>-positive cells that accumulate during vertebrate aging influence lifespan and promote age-dependent changes in several organs, and their therapeutic removal may be an attractive approach to extend healthy lifespan.

Cellular senescence is a well-established cancer defense mechanism that has also been proposed to have roles in aging and age-associated diseases, presumably through the depletion of senescent cells and progenitor cells, and the adverse actions of the senescence-associated secretory phenotype, which consists of many proinflammatory cytokines and chemokines, matrix metalloproteinases and growth factors<sup>2</sup>. Consistent with this idea is the observation that interference with senescent cell accumulation in BubR1 progredent mice delays several of the aging-associated disorders that these animals develop<sup>3</sup>. However, because progeroid syndromes do not mimic the complex degenerative changes of aging completely, the relevance of these findings has remained unclear. Furthermore, recent studies showing that senescent cells have beneficial effects in injury repair and tissue remodeling<sup>4</sup> have called into question the stereotyped view of senescence as only a driver of age-dependent pathologies, raising the specter that senescent cell clearance might remove useful cells in addition to detrimental ones. Here, we investigated the identity and physiological effects of naturally occurring senescent cells using INK-ATTAC (previously termed p16<sup>TDF2</sup>), a transgenic mouse model that expresses the p16<sup>INK4a</sup>-binding protein–camibbon 8 (p16B<sup>Camib</sup>) fusion protein and green fluorescent protein (GFP) under the control of a minimal int (also known as Ink4a/Arf) or Cdkn2a promoter fragment, transcriptionally active in senescent cells<sup>1,2,5</sup>. Unlike we have shown, in BubR1 progredent mice, INK-ATTAC ablates p16<sup>Ink4a</sup>-positive senescent cells upon administration of APO1877 (AP), a drug that activates p53-dependent Cdkn2a (Ap2k1) (Fig. 1a). Our first objective was to validate the properties of INK-ATTAC in naturally occurring p16<sup>Ink4a</sup>-positive senescent cells.

ATTAC clears senescent adipocyte progenitor cells

Our initial validation was focused on fat. We collected GFP<sup>+</sup> and GFP<sup>-</sup> cell populations from inguinal white adipose tissue (WAT) of 12-month-old ATTAC mice by FACS (Fig. 1a). GFP<sup>+</sup> cells expressed much higher levels of both p16<sup>Ink4a</sup> and FasR-Casp<sup>8</sup> than GFP<sup>-</sup> cells, as well as a broad panel of senescence markers (Fig. 1b). GFP<sup>+</sup> cells, but not GFP<sup>-</sup> cells, were also highly positive for senescence-associated b-galactosidase (SA-b-Gal, Fig. 1c). Furthermore, intact INK cells from aged, but not young ATTAC mice had SA-b-Gal activity, but less than INK of BubR1 progredent mice, a difference also reflected in INK<sup>+</sup> and INK<sup>-</sup> transcript levels (Extended Data Fig. 1a, b).

ANOVA of age-matched ATTAC mice treated weekly with AP from 12 months onward had striking loss of GFP<sup>+</sup> adipocyte progenitors relative to vehicle-injected controls, although total progenitor cell numbers remained unchanged (Fig. 1d and Extended Data Fig. 1a). SA-b-Gal staining and quantitative reverse transcription PCR (qRT-PCR) analysis of senescence markers confirmed that 12-month-old senescent WAT in INK<sup>-</sup> increased between 12 and 16 months, and that AP eliminated most of these cells (Fig. 1e and Extended Data Fig. 1d). Consistent with clearance of progenitor cells, transmission electron microscopy (TEM) on SA-b-Gal stained WAT showed that X-Crystals were present in small preadipocyte cells, but not in adipocytes, whole blood cells or adipocytes (Fig. 1f). X-Crystal crystals were found in 0.2% and 0.1% of total WAT adipocyte AP treated and control mice, respectively (Fig. 1g).

Clearance of b-Gal-positive cells prevented loss of fat mass occurring between 12 and 18 months (Fig. 1h, i) and Extended Data Fig. 1a). Age-dependent fat tissue dysfunction is characterized by decreased adipogenesis and adipocyte death<sup>6</sup>. Consistent with this, adipocyte necrosis decreased between 12 and 18 months of age (Fig. 1b), as did transcript levels of seven transcriptional regulators of adipogenesis (Fig. 1k). Treatment with AP prevented these decreases. Collectively, these data indicate that senescence contributes to age-dependent fat tissue alterations.
Senolytic agents

To stay young, kill zombies

Killing off cells that refuse to die on their own has proved a powerful anti-ageing strategy in mice. Now it’s about to be tested in humans.

By Megan Scollar
Summary: Cancer’s strong age-association

1. Mutations accumulate w/age
   ✓ Unrepaired DNA replication errors (cell division link)
   ✓ Unrepaired DNA damage

2. Epigenetic changes occur w/age
   ✓ e.g. DNA methylation decreases
   ✓ Causes largely unknown
Summary: Cancer’s strong age-association

3. Initiated cells and pre-malignant lesions (IEN) accumulate
   ✔ Probability of correct combination of mutations and epigenetic changes = CANCER
Summary: Cancer’s strong age-association

4. Decreased responsiveness of immune system w/age
   ✓ Lower immunosurveillance against IEN/cancer

Summary: Cancer’s strong age-association

5. Telomeres shorten w/age
   ✓ A trigger of cell senescence
   ✓ May contribute to age-related immunosenescence
   ✓ Critical shortening in IEN – chromosomal instability risk
Summary: Cancer’s strong age-association

6. Senescent cells accumulate w/age
   ✓ SASP
   ✓ Immunosenescence
   ✓ Chronic “smoldering” inflammation
   ✓ Promote survival & proliferation of initiated and cancer cells
   ✓ Alter tumor microenvironment = pro-cancer (e.g. mets)
THE END
The hallmarks of cancer

- Hanahan & Weingberg, Cell 2011
The Hallmarks of Aging

(Cell 2013. The hallmarks of aging. López-Otín C1, Blasco MA, Partridge L, Serrano M, Kroemer G.)
## Hallmarks of Aging

1. Telomere attrition
2. Cellular senescence
3. Genome instability
4. Stem cell exhaustion
5. Mitochondrial dysfunction
6. Epigenetic alterations
7. Altered intracellular communication (includes inflammation)
8. Deregulated nutrient sensing
9. Loss of proteostasis

## Hallmarks of Cancer

1. Sustained proliferative signaling
2. Evade growth suppressors
3. Replicative immortality
4. Resist cell death
5. Genome instability/mutation
6. Tumor-promoting inflammation
7. Avoid immune destruction
8. Angiogenesis
9. Invasion and metastasis
10. Deregulated cellular energetics
Telomere length correlates with mortality

**Fig. 2** Kaplan–Meier survival curve for the effect of telomere length on overall survival among Swedish twins. Individuals were divided into quartiles based on their telomere lengths. Longest telomere with mean length, in kilo base pairs, is 7.6 (range: 7.1–9.3), Quartile 3: 6.9 (6.6–7.1), Quartile 2: 6.3 (6.0–6.6) and shortest telomere is 5.6 (4.5–6.0). Mantel–Haenszel log-rank \( P = 0.025 \). Telomere lengths are corrected for inter-batch measurement variation.