Diseases of aging

There is still no cure for
the common birthday.
–John Glenn

Assigned reading: Chapter 8, Handbook of Aging 5th ed.

A&S300-002 Jim Lund

Diseases of Aging

- **Cancer**
- Heart disease
- Cerebrovascular disease
- Arthritis
- Osteoporosis
- Neurodegenerative disease
- Diabetes (Type II)

Cancer

- One third of people suffer from some form of cancer
- 20% of all deaths are cancer related
- In developed countries cancer care represents about 10% of total health care costs

What is cancer ?

A lineage of cells in which normal genetic control of cell proliferation and cell death have been disrupted

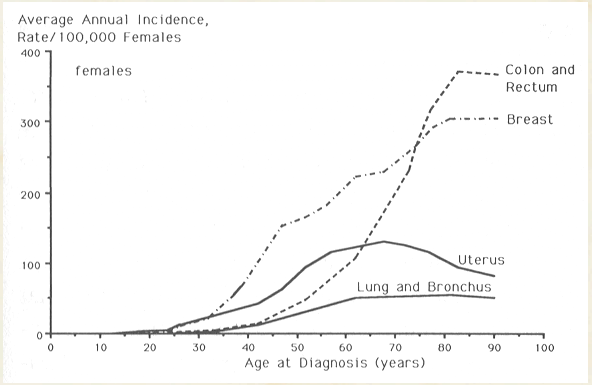
Cancer types

- Carcinomas (in which tumors arise in epithelial tissues)
- Sarcomas (in which tumor arises in mesenchymal tissue)
- Hematopoeitic & lymphoid malignancies

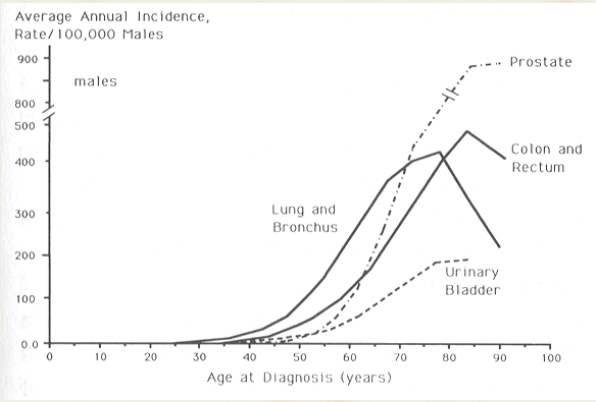
Cancer types

- Which cancer type is common varies from species to species and is often sex-dependent
- Human males: prostate cancer
- Females: breast cancer

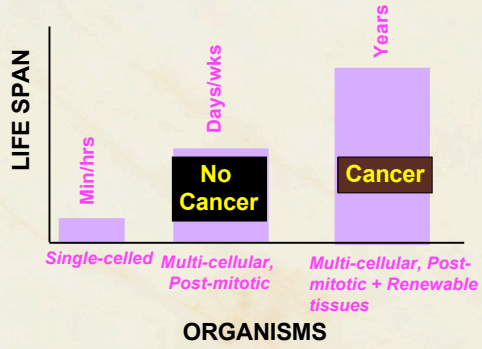
Cancer type by age, females



Cancer type by age, males



Evolution of Long-Lived Organisms



CELL DIVISION IS RISKY!!

Cancer

The bad news!

Cancer risk rises exponentially with age

Fueled by (somatic) mutations

Mutations caused by DNA damage, from endogenous and exogenous sources

Cancer

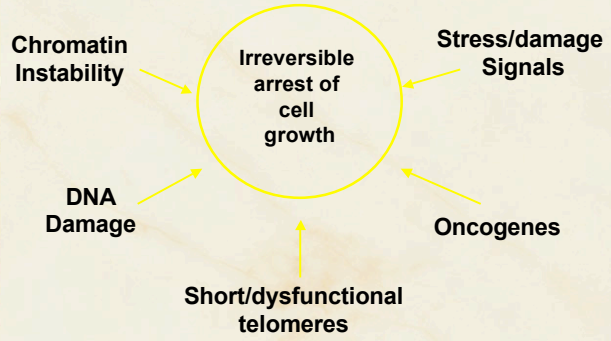
The good news!

Genes evolved to protect from cancer
(tumor suppressor genes)

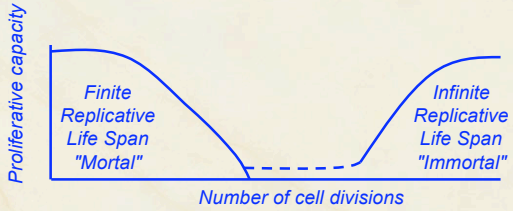
Tumor suppressor genes cause damaged cells to die or arrest growth
(undergo apoptosis or senescence)

Apoptosis and senescence = cell populations can't replenish

Cellular Senescence: Arrests Cell Growth In Response to Potential Cancer-Causing Events



First description: the Hayflick limit



EXCEPTIONS

Germ line

Early embryonic cells (stem cells)

Many tumor cells

What happens when cells exhaust their replicative life span?

Genetic causes of cancer

- Mutations to oncogenes (signalling pathways influencing death and proliferation, Ras, Bcl-2)
- Mutations to DNA repair genes (mismatch repair etc)
- Mutations to tumor suppresor genes (>50% P53, p16)

- Inactivation of tumor suppressor genes encoding p53 and pRB proteins = most common

What are oncogenes

- Genes involved in cell growth and development (growth factors, growth factor receptors etc)
- When mutated are often called protooncogenes
- Often related to viral oncogenes (e.g. src oncogene in retroviruses)
- Often highly conserved (e.g. ras found in both humans and yeast
- Mutations have a dominant phenotype and many are often required
- Mutations can be both point (bladder carcinoma) and chromosomal translocation (chronic leukemia)

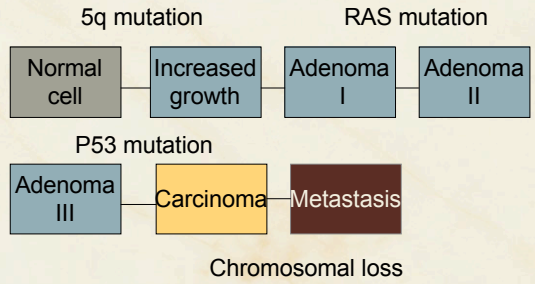
What are Tumor suppresors?

- Genes whose products block abnormal growth
- Mutations are recessive - both alleles must be lost for loss of function
- The “two hit” model of cancer progression (Knudson 1971) explains both hereditary and sporadic cases. In hereditary case 1 mutation is in germ line and 2nd in soma. E.g retinoblastoma
- Loss of TS genes often leads to several different types of cancer (50% of cancers have lost P53)
- TS genes are redundant until some other form of genetic damage arises.

Tumor Progression by Clonal Evolution

- Cancer cells are at a short term growth advantage over wild type cells
- Thus selection should lead to a preponderance of cancer cells over healthy cells
- As more mutations accumulate in cancer cells, the greater the competitive edge
- However, at the whole body level there is a cost
- In other words cancer evolves towards higher virulence within the body

Tumor Progression by Clonal Evolution - the case of colorectal cancer



Multiple hit model:
3-6 mutations required for tumorgenicity.

Mendelian Cancers

50 Mendelian disorders associated with high cancer risk

- In these cases there are multiple primary tumors, unlike sporadic
- Retinoblastoma (1/20000). Mutation to RB1 (13q) through germline. Each eye must then accumulate somatic mutation.
- RB1 mutations leads to loss of heterozygosity - homozygosity observed around region of gene

Cancer is a genetic disease:

Cancer cells are altered self by virtue of aberrant gene expression

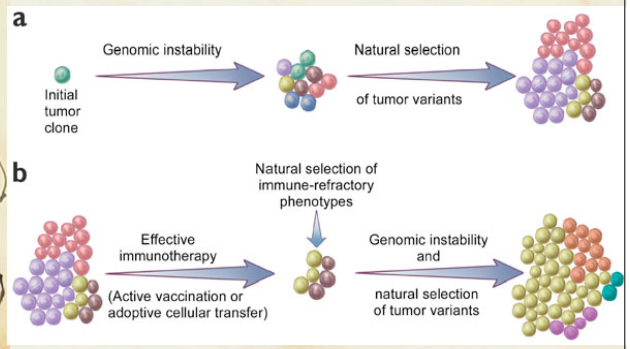
As a result of this:

Cancer cells contain proteins not found in normal cells,

or not expressed at high levels in normal cells,

or only expressed in normal cells at certain stages of development

Antigen loss



Khong & Restifo, 2002)

So if cancer is immunogenic and immunosurveillance exists…

Why does cancer occur?
Why is the immune response not successful?

In fact,

The immune response is mostly successful

but

Tumours escape from the immune response

Other age-related changes contribute to cancer

- Weakened barriers: basal membranes
- Tissue changes due to senescent cells may be procarcinogenic.

- Opposite effects:
- Tumor angiogenesis impaired in older animals

Somatic DNA mutation

- Mutation rate goes up with age:
  - $5x10^{-5}$ mutations/bp in lymphocytes
  - from 5 yr old
  - $25x10^{-5}$ mutations/bp in lymphocytes from 80 yr old
  - (from Martin et al, 1996)
- This works out to about 100 mutant genes per cell at old age.

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Effect on mean lifespan

- Curing cancer: +2 years to average human lifespan.
- Curing heart disease: +3-4 years to average human lifespan.
- Cure all disease->perhaps add 15 years to human life expectancy.