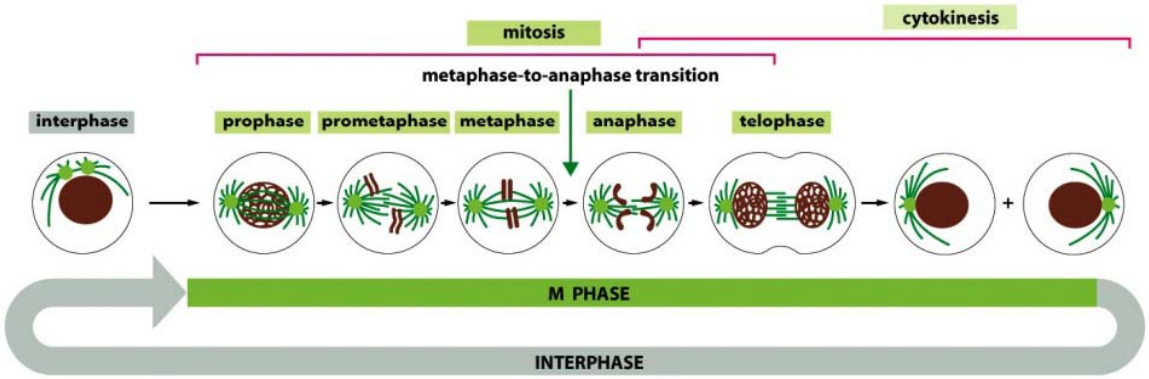
Papers for Discussion (Nov-22)

1. Elowitz MB, Levine AJ, Siggia ED, Swain PS. Stochastic gene expression in a single cell. *Science, 297:1183-1186 (2002).*

2. Hoffmann, A., Levchenko, A., Scott, M.L. and Baltimore, D. The IκB-NF-κB signaling module: temporal control and selective gene activation. *Science, 298: 1241*-1245 (2002).

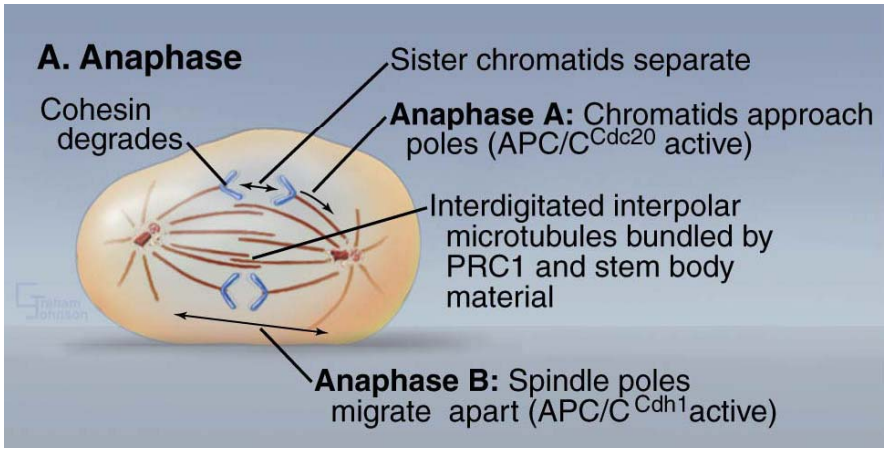
Overview of M Phase

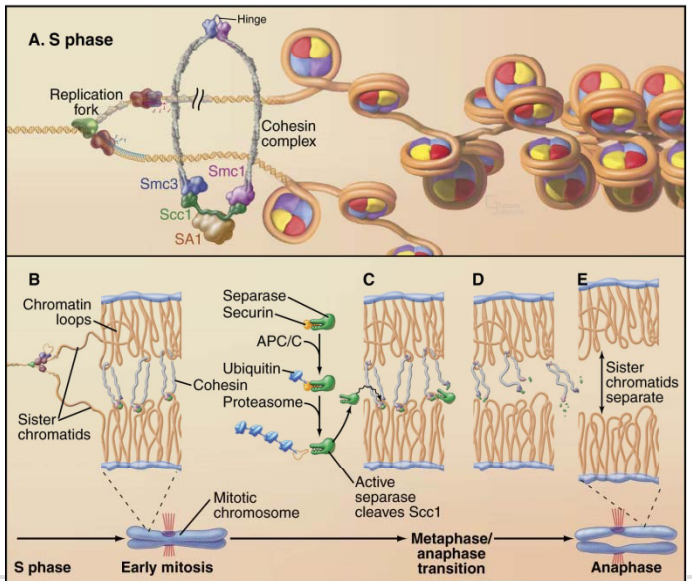


A. Interphase	B. Prophase	C. Prometaphase	D. Metaphase
Nucleus, Microtubules	Centrosome, Chromosomes	NE	
	Centrosomes separate Chromosomes condense	Nuclear envelope (NE) breaks down Chromosomes attach to spindle	Chromosomes align on spindle equator
E. Anaphase A	**F. Anaphase B**	**G. Telophase**	**H. Cytokinesis**
	CF, CS, Pole	NE, CS, CF	Midbody, CS remnant
Sister chromatids separate and move to poles	Organized central spindle (CS) assembles Cleavage furrow (CF) assembles Poles (*arrows*) separate	Cleavage furrow (CF) constricts Nuclear envelope (NE) reassembles	Chromosomes decondense Interphase microtubule network reforms Daughter cells separate

Anaphase A

- Movement of sister chromatids to the poles requires shortening of kinetochore MTs.
- Anaphase A follows activation of APC/C^{Cdc20}.
- After spindle checkpoint is turned off, APC/C^{Cdc20} triggers the degradation of securin.
- Reduced securin level allows separase to cleave cohesin.



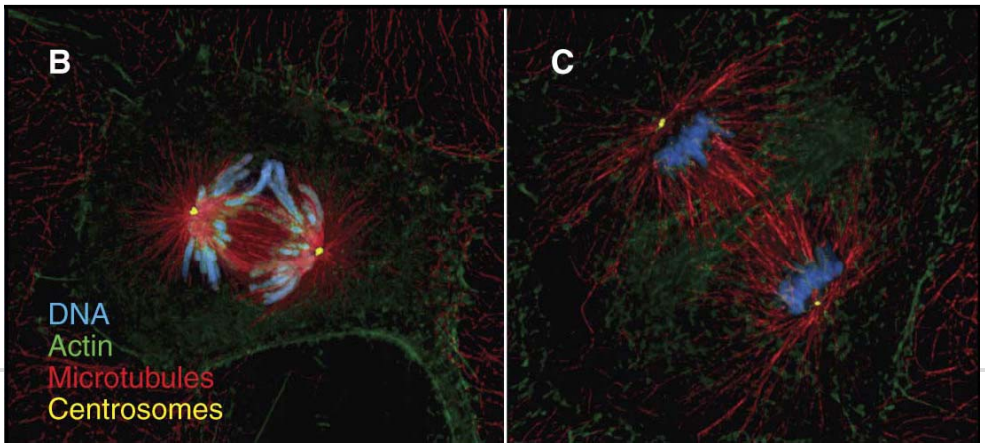


Anaphase B

- Spindle elongation pushes spindle poles apart in Anaphase B.

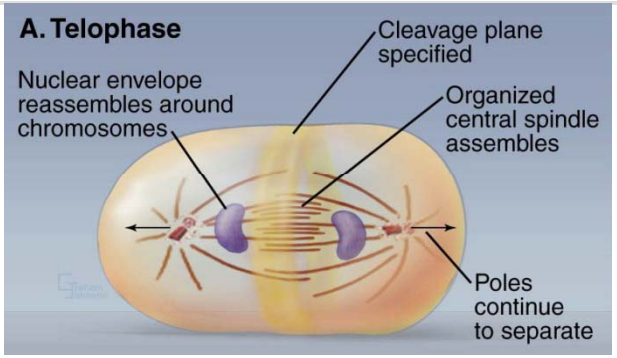
- Chromosome movement is driven by two factors
  - microtubule shortening and growth
  - microtubule flux

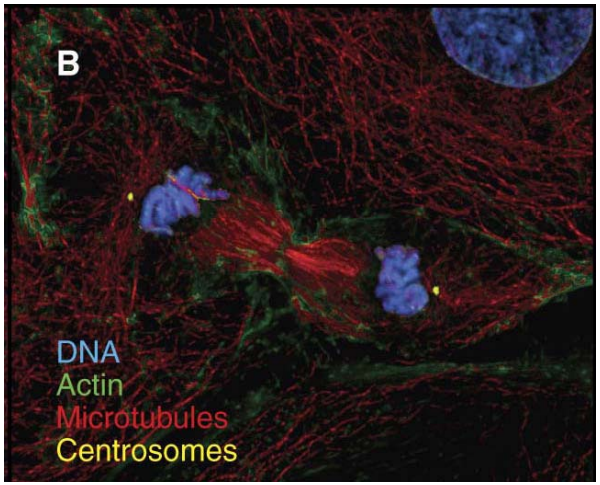
- Spindle elongation
  - Antiparallel sliding of microtubules
  - Microtubule growth
  - Spindle pole motility



Telophase

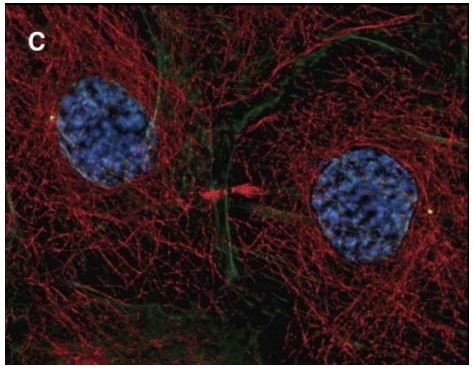
- Nuclear envelope starts to reassemble in late anaphase and is completed in telophase.
- Ran-GTP mediates nuclear envelope assembly.
- Nuclear lamina reassembles through recycling of disassembled lamin subunits.

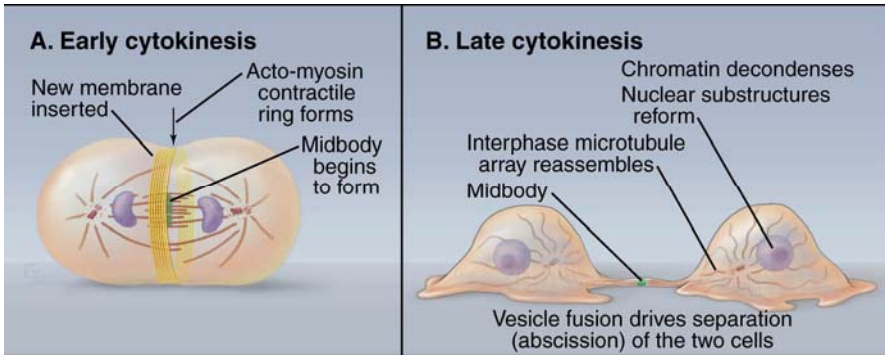




Cytokinesis (I)

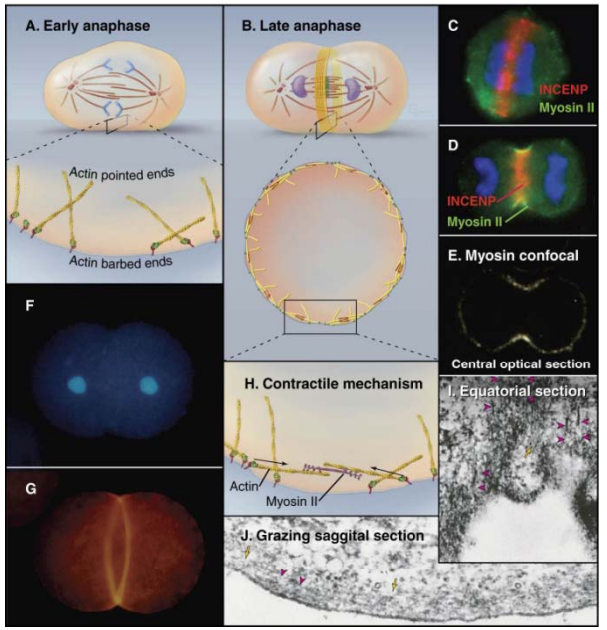
- Two daughter cells become separated through cytokinesis.
- Formation of the contractile ring requires actin and myosin-II.
- Separation of two daughter cells is accompanies by constriction and disassembly of the contractile ring.

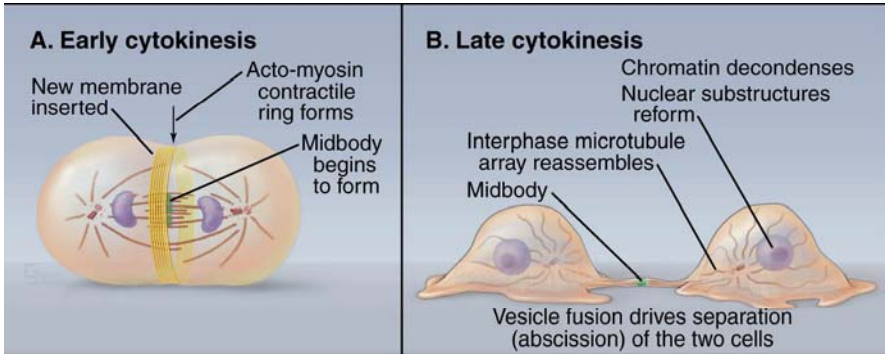




Cytokinesis (II)

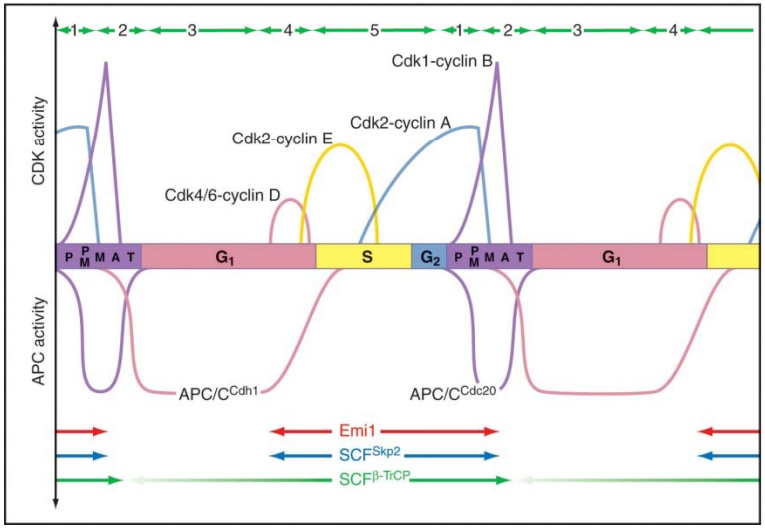
- Cytokinesis requires membrane addition and abscission.
- Secretory vesicles from the Golgi provides new membrane.
- Midbody contains many proteins involved in membrane trafficking.
- Intracelluar bridges may remain open to connect cells.





Exit From Mitosis

- Cdk1 must be inactivated for exit from mitosis.
- Much of what is known of exit from mitosis comes from budding yeast.
- Exit from mitosis in yeasts is mediated by the MEN GTPase.
- Lowered Cdk activities allow the release of MEN GTPases.
- Released MEN GTPases activate Cdc14p, which inhibits Cdks.



Engineering Molecular Cell Biology
Lecture 24, Fall 2010

Cancer

Ref: Alberts et al, *Mol. Biol. Cell, 5e, Chapter 20*

Outline

- Overview
- Preventable causes of cancer
- Genetic basis of cancer
- Cancer treatment
- Current status

Overview

- Cancer is the second leading cause of death.
  - ~11.4 million survivors in US (2006, NCI)
- Cancer has a unique importance to cell biology in helping us to understand regulation of cell behavior.
- Many basic discoveries in cell biology are closely associated with cancer research.
  - DNA repair
  - Cell signaling
  - Cell cycle
  - Apoptosis

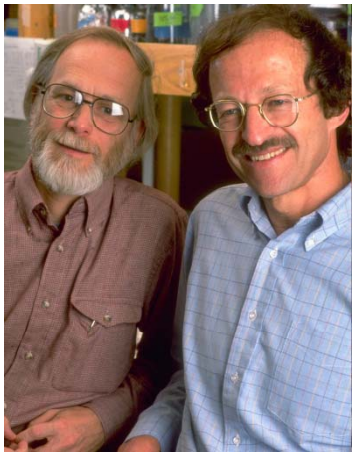
Number of deaths for leading causes of death

- Heart disease: 616,067
- Cancer: 562,875
- Stroke (cerebrovascular diseases): 135,952
- Chronic lower respiratory diseases: 127,924
- Accidents (unintentional injuries): 123,706
- Alzheimer's disease: 74,632
- Diabetes: 71,382
- Influenza and Pneumonia: 52,717
- Nephritis, nephrotic syndrome, and nephrosis: 46,448
- Septicemia: 34,828

Source: Deaths: Final Data for 2007, table B (/NCHS/data/nvsr/nvsr58/nvsr58_19.pdf)

A Milestone in Cancer Research

- In 1979, Michael Bishop and Harold Varmus at UCSF discovered the first human oncogene c-Src.
- Their discovery opened a new era of cancer research in searching for the underlying molecular and cellular mechanisms.
- Research over the past three decades produced enormous amount of information about the molecular and cellular bases of cancer.



Michael Bishop & Harold Varmus

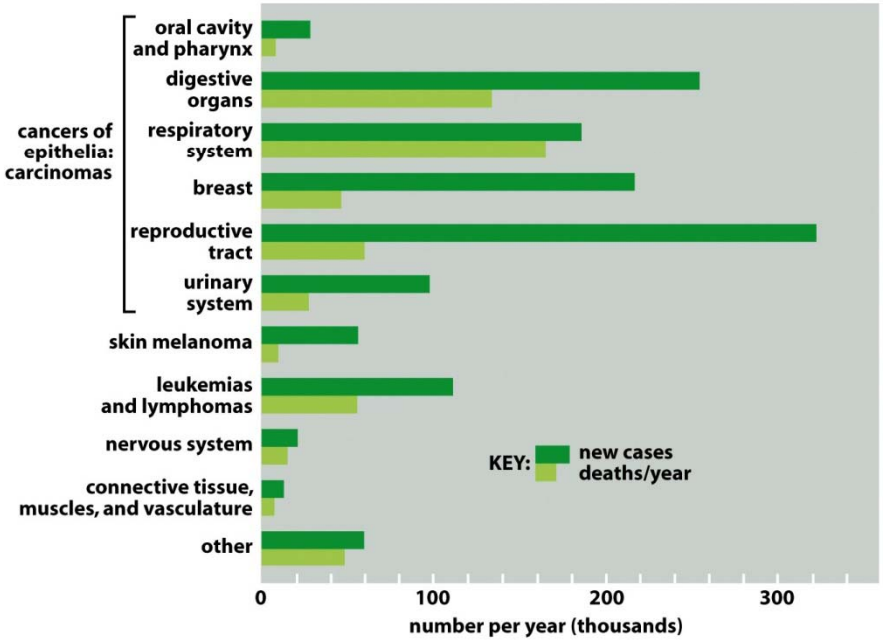
Some Basic Properties of Cancer Cells

- Cancer cells escape normal regulation mechanisms to proliferate at the expense of neighboring cells.
- Uncontrolled cell proliferation results in tumors.
- A tumor is considered a cancer only if it is malignant, i.e. its cells invade and colonize surrounding tissues.
- Cancer is a microenvironment process.

Different Origins of Cancer

- Cancers originate from specific tissues:

  - adenocarcinoma: glandular tissue
  - blastoma: embryonic tissue of organs
  - carcinoma: epithelial tissue
  - leukemia: blood cells
  - lymphoma: lymphatic tissue
  - myeloma: bone marrow
  - sarcoma: connective tissue (bone, cartilage, muscle)

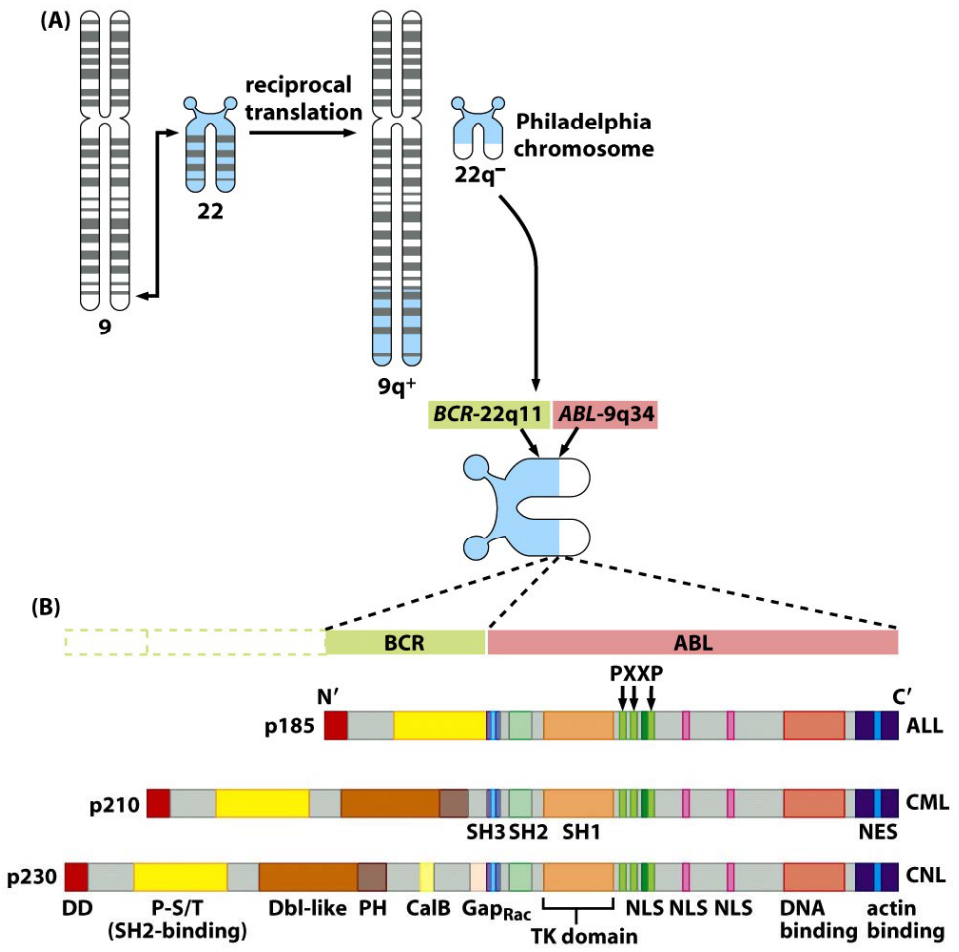


- Epithelium is the sheet of cells that cover the inner or outer surface of a structure.

- ~80% of human cancers are carcinomas.

Chronic Myelogenous Leukemia (II)

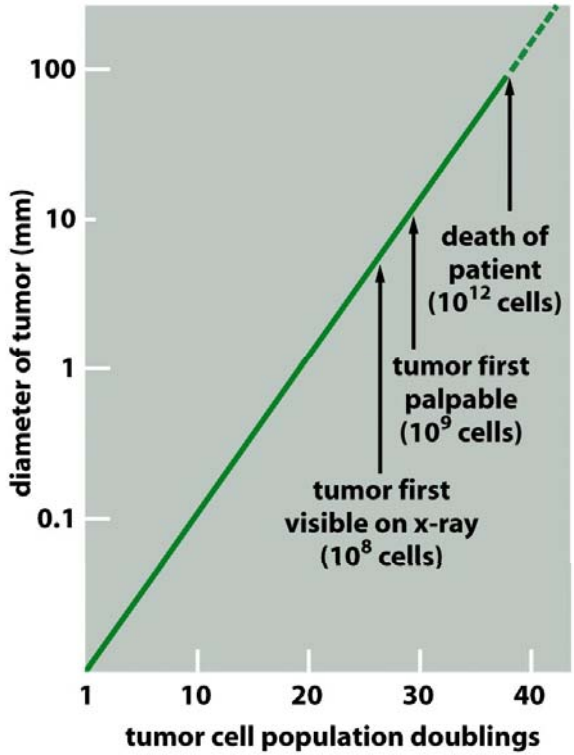
- Philadelphia chromosome (1960)
- Reciprocal translocations of chromosome 9 & 22
- Identification of Bcr-Abl gene (1982)
- Bcr-Abl functions as a constitutively active tyrosine kinase (1984)
- Bcr-Abl actives many pathways related to cell proliferation



Weinberg, R. A. *Biology of Cancer*, 2007

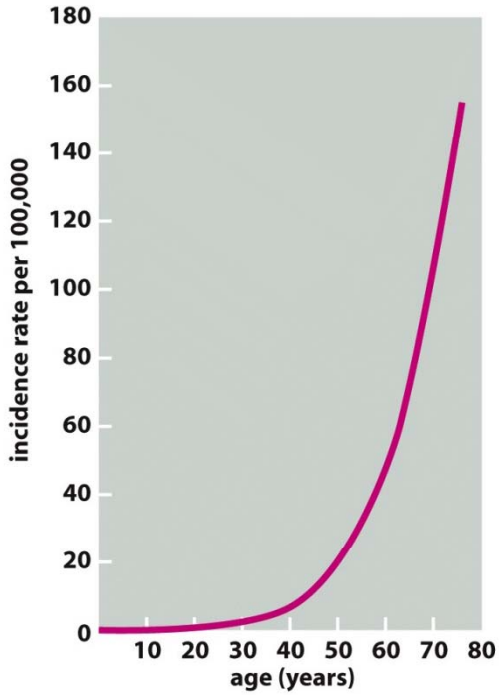
Cancers From a Single Abnormal Cell

- Metastatic cancer cells can be traced to a primary tumor.
- Tumors often can be traced to a single abnormal cell.
- By the time of detection, many human cancers have been developing for years.



Development of Cancer (I)

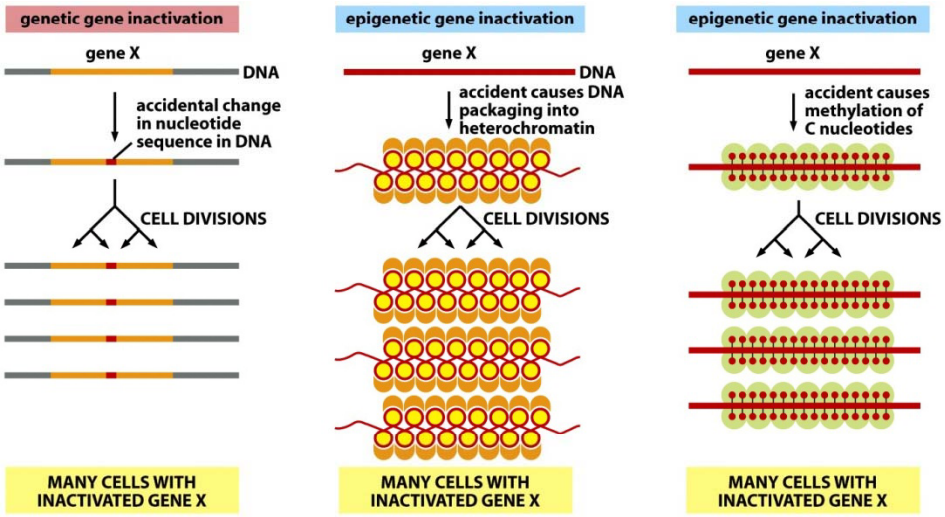
- Genetic mutations occur naturally.
  - Mutation rate: 1 out of 10^6 cell divisions
  - 10^{16} cell divisions $\rightarrow$ 10^{10} mutations
- Cancer development requires multiple mutations that accumulate over time.
- Genetic changes $\rightarrow$ changes in DNA
  Epigenetic changes $\rightarrow$ changes in gene expression
- Cancer cells emerge as "winners" of natural selection.



Development of Cancer (II)

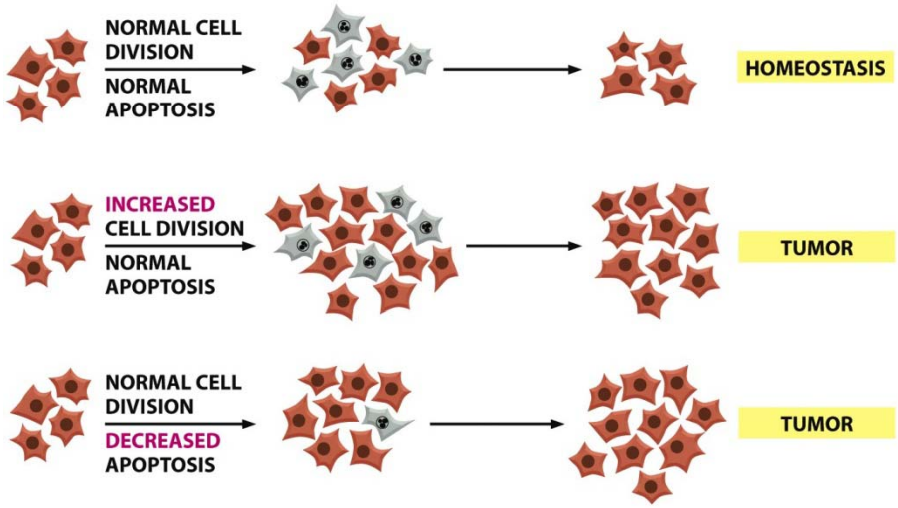
- Epigenetic changes are inheritable and play important roles in cancer development.

- Two main types of epigenetic changes
  - Modifications of chromatin structure
  - Changes in DNA methylation



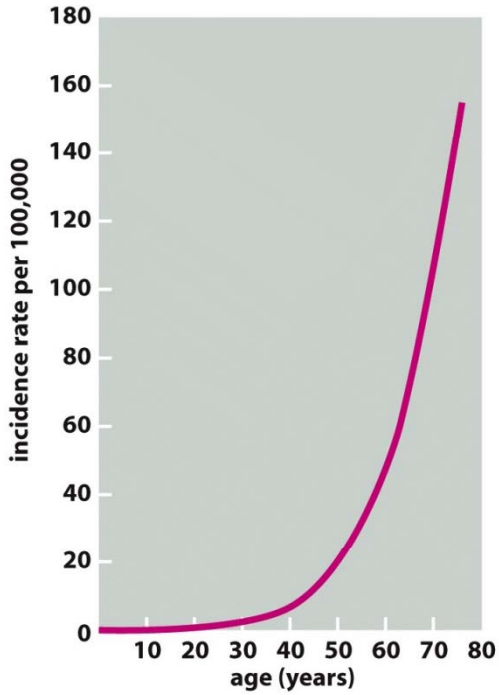
Development of Cancer (III)

- Initial development of cancer is gradual.
- Abnormal cells gradually accumulate more mutations or epigenetic changes during initial development.
- Cancer growth depends on defective control of cell division, cell differentiation, and apoptosis.



Development of Cancer (IV)

- Certain cancers may take decades to develop before symptoms become detectable.
- This offers the possibility of early detection and intervention.



Cancer Cells Are Genetically Unstable

- Human cancer cells accumulate genetic changes at much higher rates than normal cells.
  - Defective DNA damage checkpoints
  - Defective DNA repair mechanisms
  - Chromosome abnormalities
  - Epigenetic changes

- Cancer development relies on an optimized level of genetic instability.

Cancer Stem Cells (I)

- Like normal tissues, many cancers are organized in a hierarchical way.

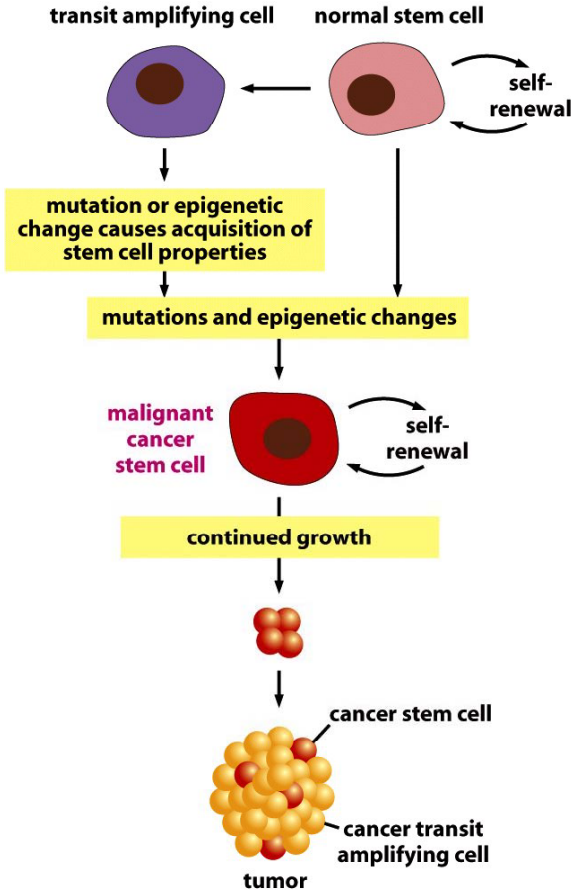
- A small population of cancer stem cells is capable of infinite renewal and is responsible for maintaining the cell population of a tumor.

- Most tumor cells have limited capacity of self-renewal.

  - There is a very small chance (~1%) that a random chosen cell from a tumor will generate a tumor.

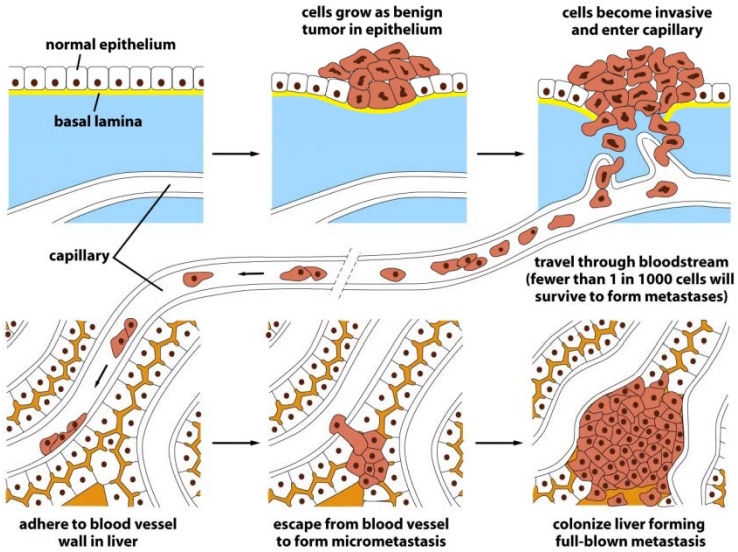
Cancer Stem Cells (II)

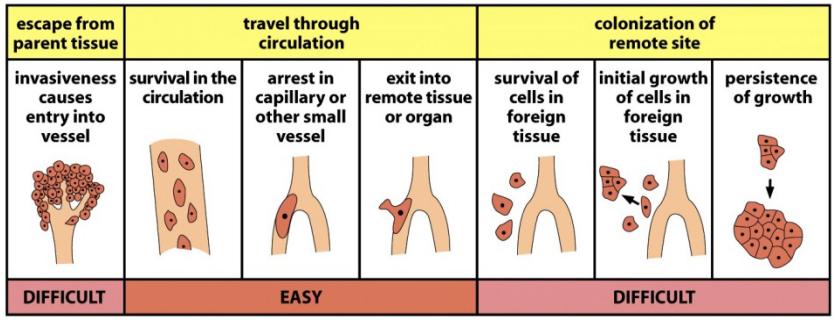
- Cancer stem cells likely result from epigenetic changes.
- There are strong evidences that some tumors evolve from abnormal tissue stem cells.
  - Only tissue stem cells stay long enough to accumulate mutations required for a cancer.
- Another possible source of cancer stem cells is through changes of a proliferating cell.



Metastasis

- Metastasis is responsible for 90% of cancer-related patient deaths.
- Metastatic cancers can no longer be contained by surgery or irradiation.
- Metastatic cancer cells must be able to survive and proliferate in new environments, a rare process called colonization.
- Could the metastatic cells be cancer stem cells?





Angiogenesis

- Tumors recruit blood supply for its survival and growth by secreting angiogenic signals.

  Judah Folkman
  http://www.childrenshospital.org/cfapps/research/data_admin/Site105/mainpageS105P0.html

- Secreted signals attract endothelial cells and stimulate growth of new blood vessels.

- Induced vessels are irregular and leaky.

- Induced vessels are potential targets for cancer therapy.

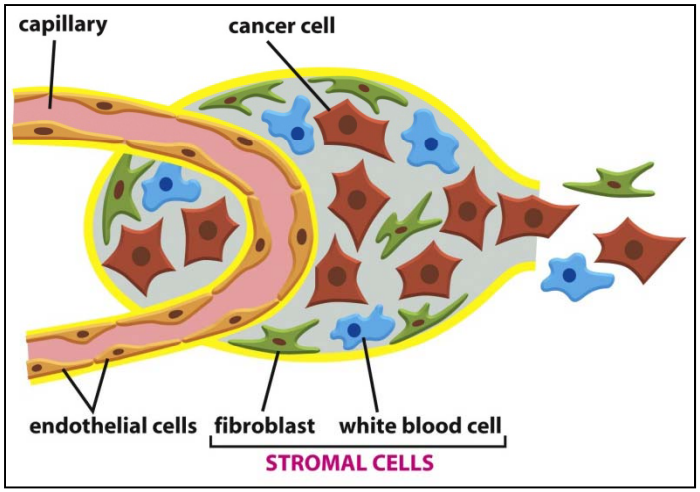
Microenvironment in Cancer Development

- Microenvironment of cancer plays a critical role in determining its development.

  Mina Bissell

  http://www.lbl.gov/LBL-Programs/lifesciences/BissellLab/main.html

- Supportive tissues (stroma) of cancer actively collaborate with cancer cells.

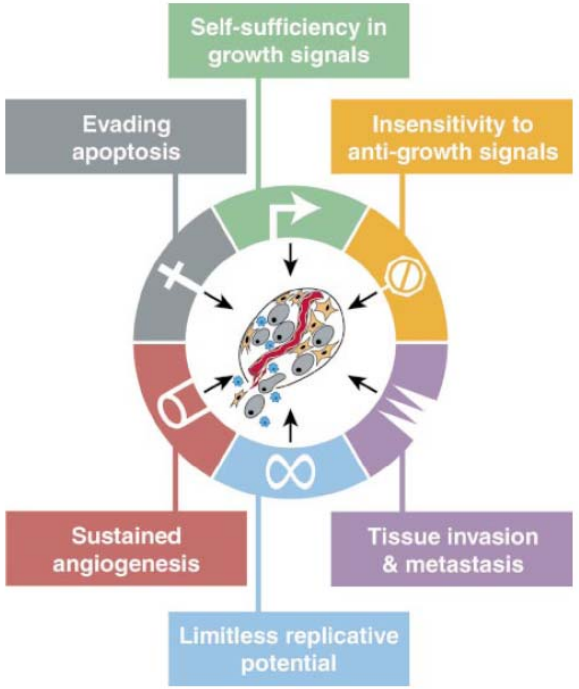


- Composition of the stroma
  - fibroblast
  - myofibroblast
  - inflammatory white blood cells
  - endothelial cells of blood and lymphatic vessels

- Cancer cells and stromal cells evolve together.

Six Hallmarks of Cancer

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Limitless replicative potentials
- Sustained angiogenesis
- Tissue invasion & metastasis



Hanahan & Weinberg,
The hallmarks of cancer, *Cell*, 100:57, 2000.

Preventable Causes of Cancer

Environmental and Lifestyle Factors

- Mutations can not be completely avoided due to limitations of the accuracy of DNA replication and repair.
- Environmental and lifestyle factors play an important role in cancer development.
- Different cancers have different risk factors.

environmental and lifestyle factors	cancer	% total cases
• occupational exposure	various types	1–2
• tobacco related	lung, kidney, bladder	24
• diet: low in vegetables, high salt, high nitrate	stomach, esophagus	5
• diet: high fat, low fiber, fried and broiled foods	bowel, pancreas, prostate, breast	37
• tobacco and alcohol	mouth, throat	2

Carcinogens, Viruses, & Infections

- Many cancer-causing factors induce mutations and DNA damages.
- Viruses and other infections play important roles in cancer development.

- **VINYL CHLORIDE:**
  liver angiosarcoma
- **BENZENE:**
  acute leukemias
- **ARSENIC:**
  skin carcinomas, bladder cancer
- **ASBESTOS:**
  mesothelioma
- **RADIUM:**
  osteosarcoma

Table 20–1 Viruses Associated with Human Cancers

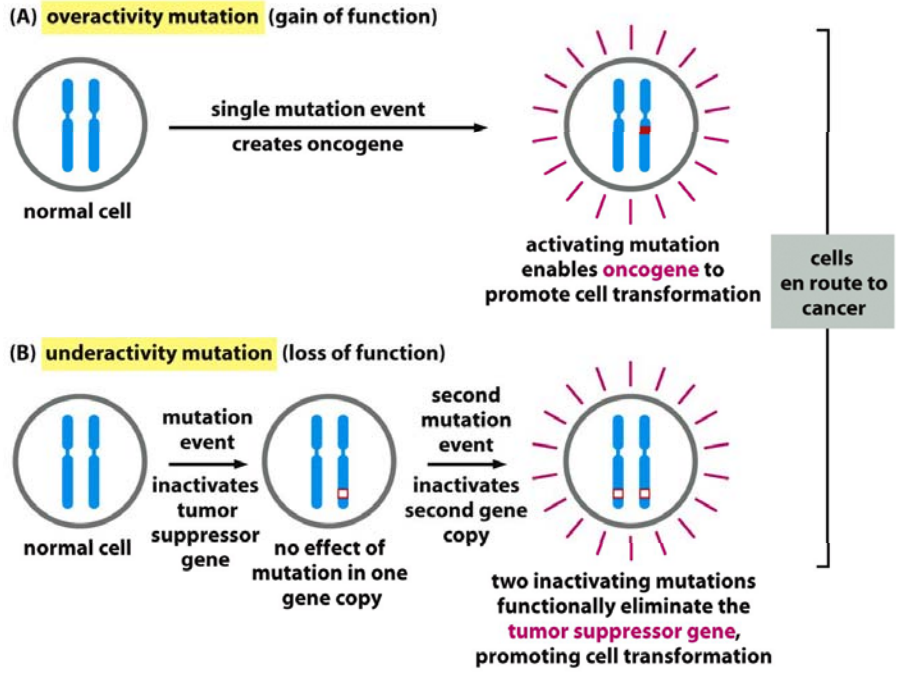
VIRUS	ASSOCIATED CANCER	AREAS OF HIGH INCIDENCE
DNA viruses		
Papovavirus family		
Papillomavirus (many distinct strains)	warts (benign) carcinoma of the uterine cervix	worldwide worldwide
Hepadnavirus family		
Hepatitis-B virus	liver cancer (hepatocellular carcinoma)	Southeast Asia, tropical Africa
Hepatitis-C virus	liver cancer (hepatocellular carcinoma)	worldwide
Herpesvirus family		
Epstein–Barr virus	Burkitt's lymphoma (cancer of B lymphocytes) nasopharyngeal carcinoma	West Africa, Papua New Guinea Southern China, Greenland
RNA viruses		
Retrovirus family		
Human T-cell leukemia virus type I (HTLV-1)	adult T-cell leukemia/ lymphoma	Japan, West Indies
Human immuno-deficiency virus (HIV, the AIDS virus)	Kaposi's sarcoma	Central and Southern Africa

For all these viruses, the number of people infected is much larger than the numbers who develop cancer: the viruses must act in conjunction with other factors. Moreover, some of the viruses contribute to cancer only indirectly; HIV, for example, destroys helper T lymphocytes, which allows a herpes virus to transform endothelial cells. Similarly, hepatitis-C virus causes chronic hepatitis, which promotes the development of liver cancer.

Genetic Basis of Cancer

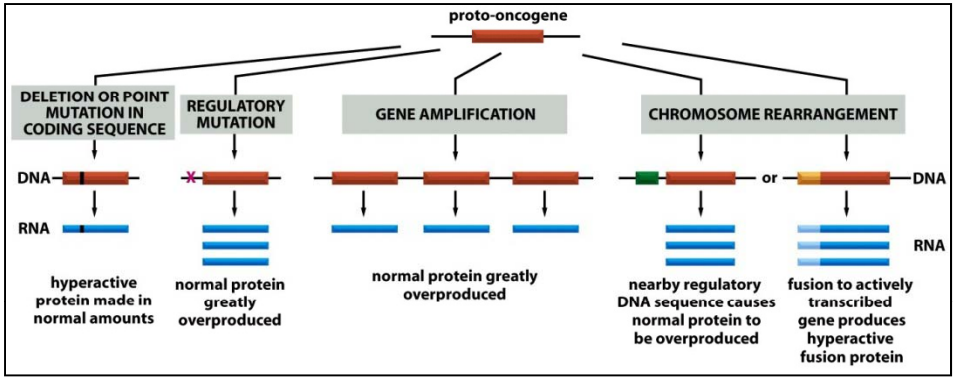
Oncogenes & Tumor Suppressors (I)

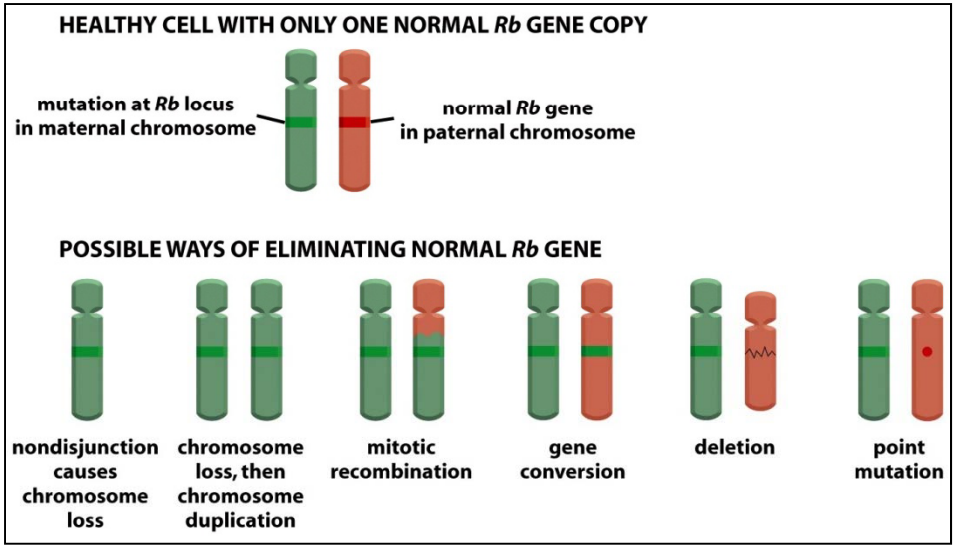
- Two classes of cancer-critical genes
  - Proto-oncogenes
  - Tumor suppressor genes
- Mutants of proto-oncogenes are called oncogenes.
- Mutations of oncogenes and tumor suppressor genes can have similar effects.



Oncogenes & Tumor Suppressors (II)

- Oncogenes can be activated in many ways.
- Tumor suppressor genes can be lost in many ways.





Cancer Treatment

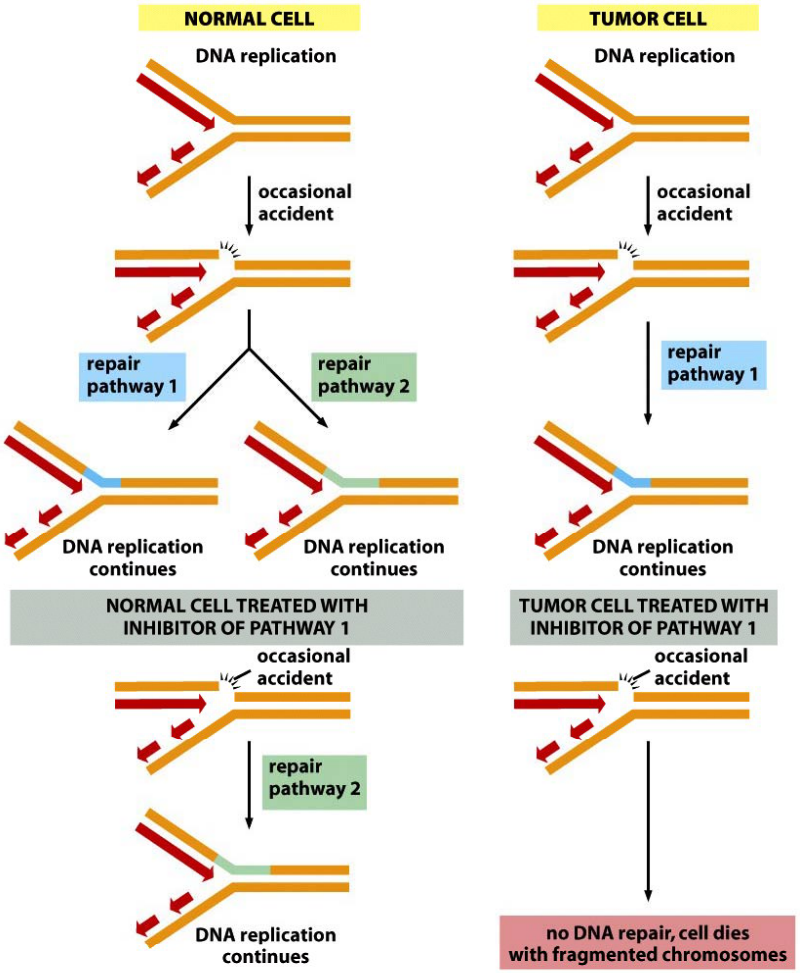
Traditional Cancer Therapy

- Traditional anticancer therapy draws on the weakened capabilities of cancer cell to survive DNA damages.

- Problems
  - Less specific to cancer stem cells
  - Drug resistance
  - Induced resistance to apoptosis
  - Other side effects

Rational Treatment of Cancer (I)

- More specific strategies based on genetic instability of cancer cells.
- More specific delivery of anticancer drugs using monoclonal antibodies.
- Development of specific small molecules.



Rational Treatment of Cancer (II)

- Cancer treatment by targeting angiogenesis.
- Cancer treatment by inducing immune responses.
- Cocktail approaches to suppress drug resistance.
- Genomic profiling makes specific treatment strategies possible.
- No magic solution. Still a long way to go…

Current Status

Current Status (I)

- The rate of cancer incidence starts to decline since the early 1990s.

- However, incidence rates of certain types of cancer are rising, e.g.
  - liver, pancreas, kidney cancer
  - leukemia
  - childhood cancers
  - brain cancers

Figure D1. Rates of new cases of all cancers, delay-adjusted cancer incidence: 1975-2005

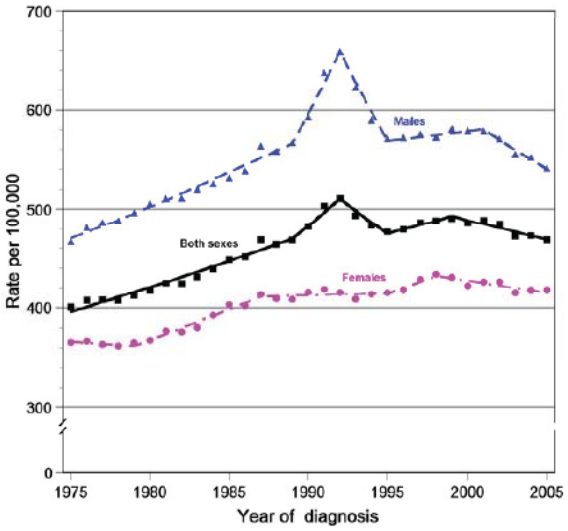


Figure E2. Death rates for common cancers: 1975-2005

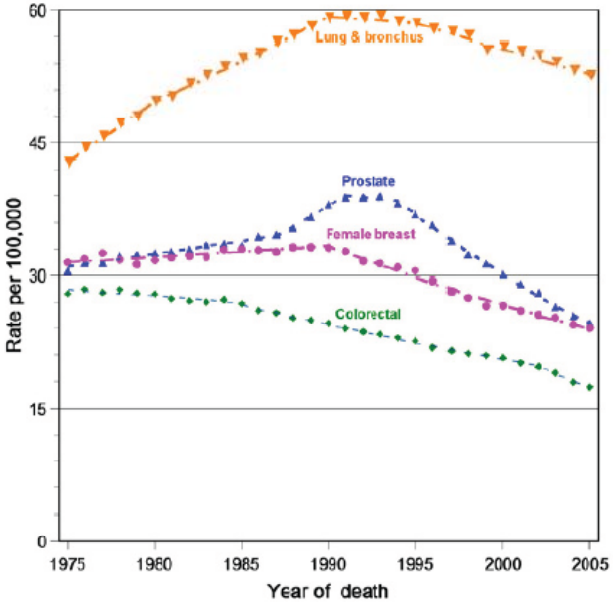
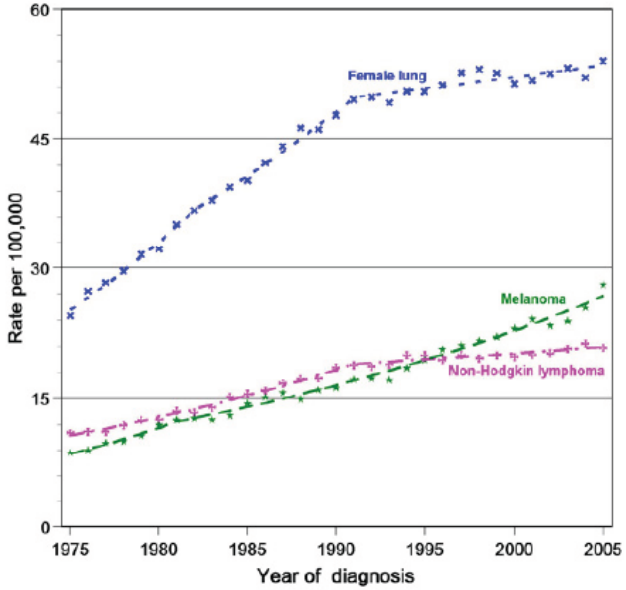


Figure D4. Rates of some common cancers that are increasing, delay-adjusted cancer incidence: 1975-2005



Cancer trends progress report, NCI, 2007

Current Status (II)

- Death rates of common cancers are declining.
- Overall death rates are declining.
- Declining of death rates is slow.

Figure E2. Death rates for common cancers: 1975-2005

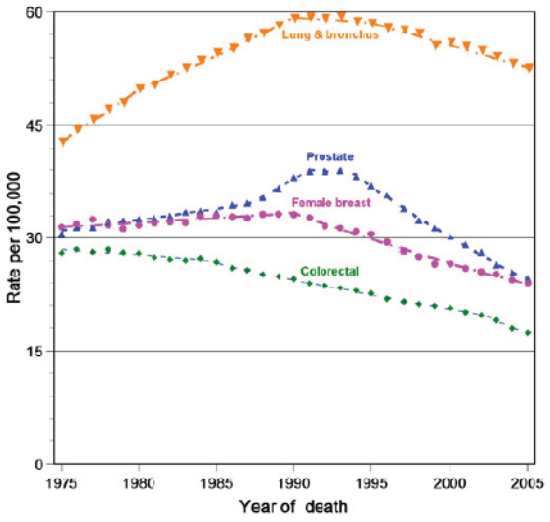


Figure L1. 5-year relative survival rates: 1975-2000

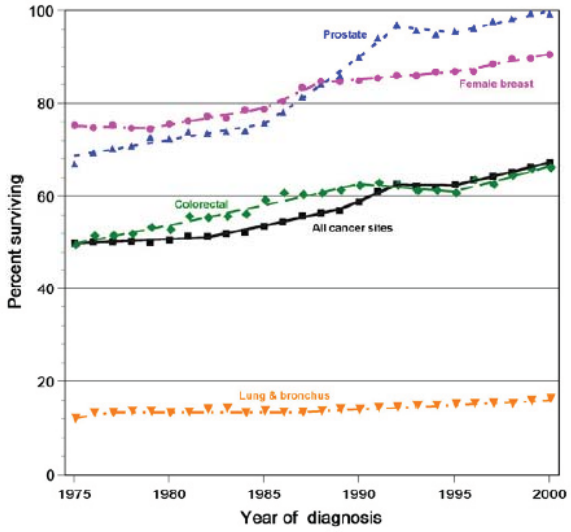
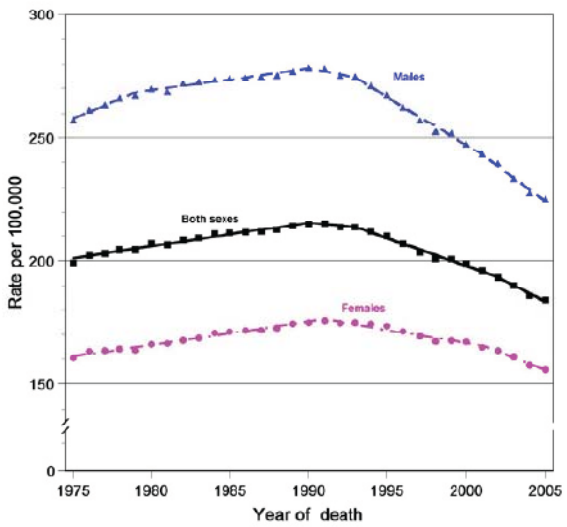


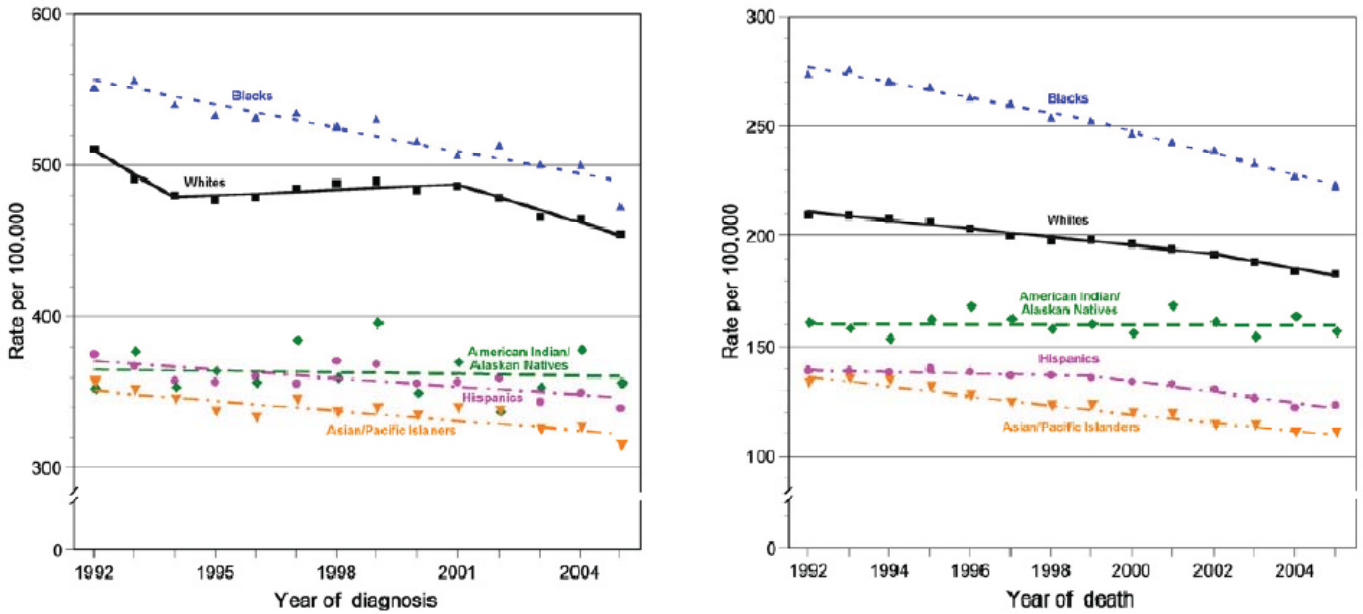
Figure E1. Death rates for all cancers: 1975-2005



Cancer trends progress report, NCI, 2007

Variations Among Different Ethnic Groups

Figure D3. Rates of new cases of all cancers, by race / ethnicity: 1992-2005



Cancer trends progress report, NCI, 2007

Questions?

Supplementary Reading

- Hanahan & Weinberg, The hallmarks of cancer, *Cell*, 100:57, 2000.
- *Cancer trends progress report-2009/2010 update*, National Cancer Institute. http://progressreport.cancer.gov/
- Weinberg, RA, *The Biology of Cancer*, Garland Science, 2007.
- Gascoigne KE & Taylor SS, Cancer cells display profound intra- and interline variation following prolonged exposure to antimitotic drugs, *Cancer Cell* 2008, 14:111-122.