An Introduction to Cancer Biology

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Learning Objectives

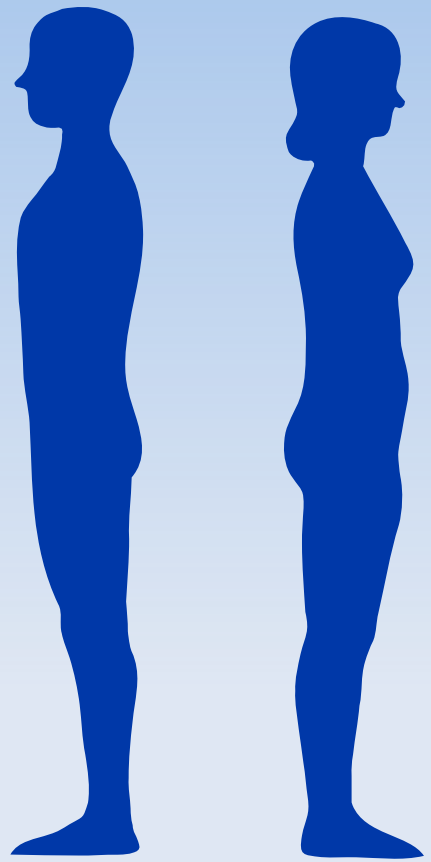
- The students will be able to:
  - Identify the **3** most prevalent cancers for a person of their gender
  - Define cancer
  - Explain why cancer is a genetic disease even though its heritability is rather low
  - Compare the functions of oncogenes and tumor suppressor genes
  - Explain why tumor suppressors are often the 1st genes mutated in a developing cancer
  - List the Six Hallmarks of Cancer
  - Describe the advantages of using modern, targeted cancer therapies

US Mortality, 2003

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	685,089	28.0
2.	**Cancer**	**556,902**	**22.7**
3.	Cerebrovascular diseases	157,689	6.4
4.	Chronic lower respiratory diseases	126,382	5.2
5.	Accidents (Unintentional injuries)	109,277	4.5
6.	Diabetes mellitus	74,219	3.0
7.	Influenza and pneumonia	65,163	2.7
8.	Alzheimer disease	63,457	2.6
1.	Nephritis	42,453	1.7
10.	Septicemia	34,069	1.4

2006 Estimated US Cancer Cases*

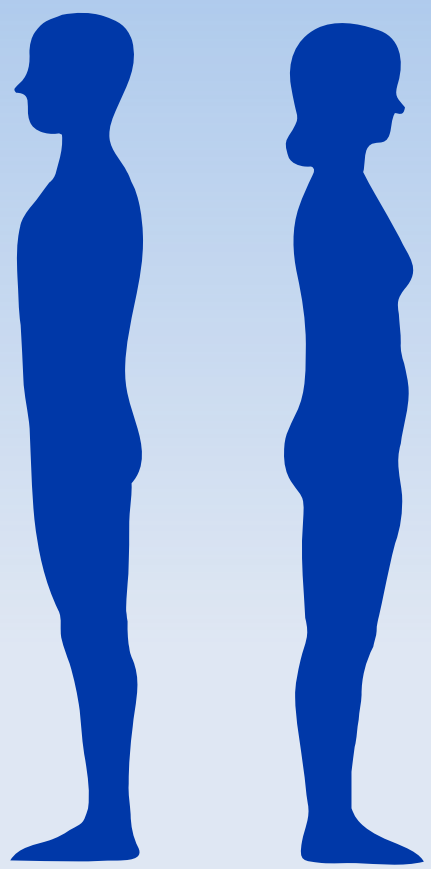
Men 720,280		Women 679,510	
Prostate	33%	31%	Breast
Lung & bronchus	13%	12%	Lung & bronchus
Colon & rectum	10%	11%	Colon & rectum
Urinary bladder	6%	6%	Uterine corpus
Melanoma of skin	5%	4%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	4%	4%	Melanoma of skin
Kidney	3%	3%	Thyroid
Oral cavity	3%	3%	Ovary
Leukemia	3%	2%	Urinary bladder
Pancreas	2%	2%	Pancreas
All Other Sites	18%	22%	All Other Sites



***Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.**
Source: American Cancer Society, 2006.

2006 Estimated US Cancer Deaths*

Men 291,270		Women 273,560	
Lung & bronchus	31%	26%	Lung & bronchus
Colon & rectum	10%	15%	Breast
Prostate	9%	10%	Colon & rectum
Pancreas	6%	6%	Pancreas
Leukemia	4%	6%	Ovary
Liver & intrahepatic bile duct	4%	4%	Leukemia
Esophagus	4%	3%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	3%	3%	Uterine corpus
Urinary bladder	3%	2%	Multiple myeloma
Kidney	3%	2%	Brain/ONS
All other sites	23%	23%	All other sites



ONS=Other nervous system.
Source: American Cancer Society, 2006.

What is cancer?

- Abnormal cell growth (**neoplasia**)
- **Malignant** as opposed to benign
  - **Benign:** slow growth, non-invasive, no metastasis
  - **Malignant:** rapid growth, **invasive**, potential for metastasis

Is cancer a heritable disease?

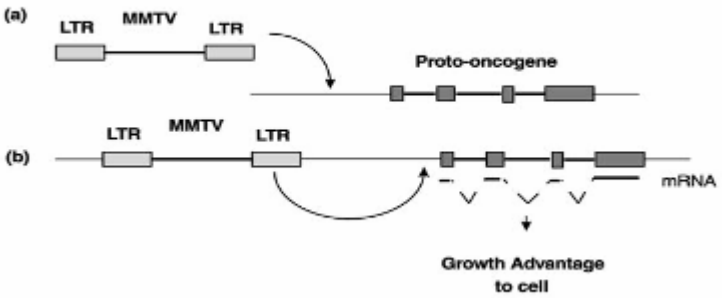
- There are heritable cancer syndromes
- The majority of cancers, however, are not familial
- Cancer is a genetic disease, but the majority of mutations that lead to cancer are **somatic**

What causes the mutations that lead to cancer?

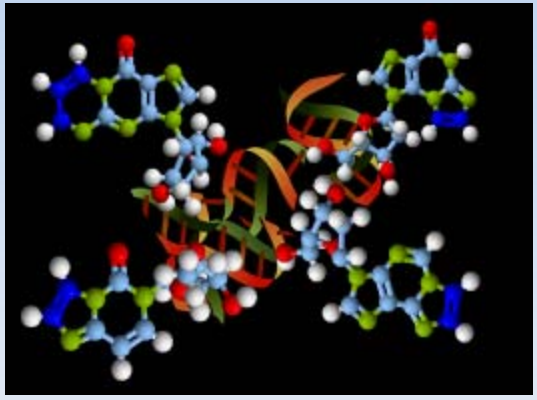
- Viruses: HPV --> cervical cancer
- Bacteria: H. pylori --> gastric cancer
- Chemicals --> B[a]P --> lung cancer
- UV and ionizing radiation --> skin cancer

- What do these agents have in common?

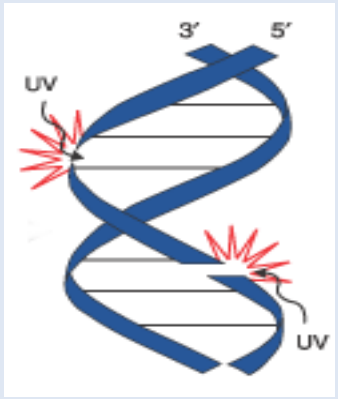
Mutagens



- Viruses: insertional mutagenesis



- Chemicals: DNA adducts



- UV and ionizing radiation: single and double strand DNA breaks

What types of genes get mutated in cancer?

- **Oncogenes** are activated
  - Normal function: cell growth, gene transcription
- **Tumor suppressor** genes are inactivated
  - Normal function: DNA repair, cell cycle control, cell death

Phenotype of a cancer cell

- **The Six Hallmarks of Cancer**
  - Self-sufficient growth signals
    - Constitutively **activated** growth factor signalling
  - Resistance to anti-growth signals
    - **Inactivated** cell cycle checkpoint
  - Immortality
    - **Inactivated** cell death pathway

Phenotype of a cancer cell (cont'd)

- **The Six Hallmarks of Cancer**
  - Resistance to cell death
    - **Activated** anti- cell death signalling
  - Sustained angiogenesis
    - **Activated** VEGF signalling
  - Invasion and metastasis
    - Loss of cell-to-cell interactions, etc.

p53—a classic tumor suppressor

- “The guardian of the genome”
- Senses genomic damage
- Halts the cell cycle and initiates DNA repair
- If the DNA is irreparable, p53 will initiate the cell death process

Rb—a classic tumor suppressor

- Rb binds to a protein called E2F1
- E2F1 initiates the G1/S cell cycle transition
- When bound to Rb, E2F1 can't function
- Thus, Rb is a crucial cell cycle checkpoint

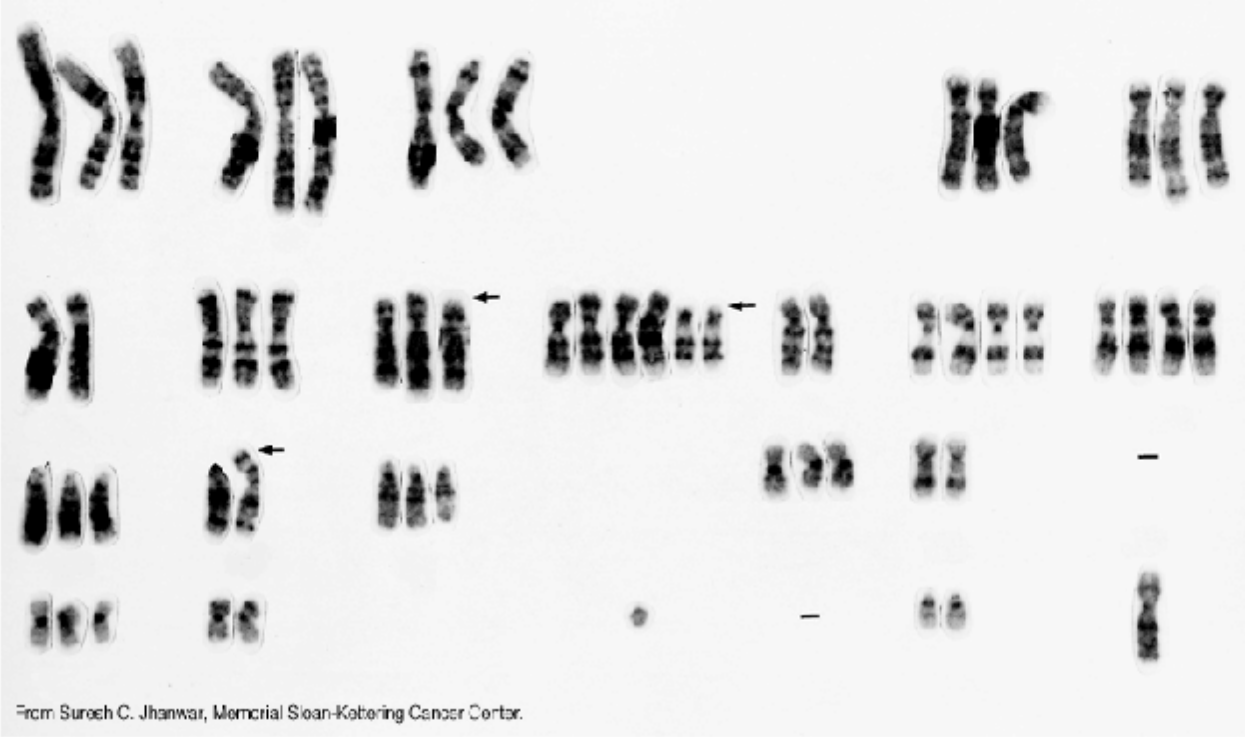
Tumor suppressors

- “Guardian(s) of the genome”
- Often involved in maintaining genomic integrity (DNA repair, chromosome segregation)
- Mutations in tumor suppressor genes lead to the “mutator phenotype”—mutation rates increase
- Often the 1st mutation in a developing cancer

Chromosomal Instability

Karyotype of a tumor cell

A highly abnormal complement of chromosomes (60 chromosomes instead of normal 46 chromosomes)



From Suresh C. Jhanwar, Memorial Sloan-Kettering Cancer Center.

HER2/neu—an oncogene

- A growth factor receptor
- 25-30% of breast cancers over-express HER2/neu
- Which hallmark of cancer does this lead to?
- Herceptin is used as a treatment

What can cancer therapies target?

- Classic cancer therapies target **rapidly dividing cells**
- **Target the DNA**
  - **Ionizing radiation**
  - **Chemotherapy**
- **Many side effects**
  - **Hair loss**
  - **Weakened immune system**
  - **Problems with GI tract**

What can cancer therapies target?

- **A person's immune system will not target tumor cells because they appear to be “self”**
- **Some new therapies focus on activating one's immune system against a cancer**

What can cancer therapies target?

- **Modern, targeted therapies attack specific proteins that are abnormally expressed in a tumor**
- **May block over-expressed growth factor receptors --> Herceptin**
- **Generally, there are few side effects since these therapies are specifically targeted to cancer cells**