Chapter 12
Genes and Cancer
History of Cancer

- Mutations lead to variation and most of the time this is a good thing, but...sometimes the result of a mutation is negative.

- Cancer has long been a part of human existence.

- For an introduction to a timeline of cancer visit: http://www.cancerquest.org/cancer-timeline-introduction
12.1 Cancer Is a Genetic Disorder of Somatic Cells

- Cancer is a complex disease characterized by two main properties:
  - Uncontrolled cell division (leads to tumors)
  - Tumors can be **benign** - do not invade other tissues or can be **metastatic** - spread to other sites in the body

- In the US each year, more than one million new cancer cases are diagnosed and approximately 500,000 people will die from cancer.
- 1 in 3 persons will get cancer in their lifetime.
**New Cases of Cancer in the US, 2009**

**Table 12.1** Estimated New Cases of Selected Cancers in the United States, 2009

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sites (except skin)</td>
<td>1,479,350</td>
</tr>
<tr>
<td>Breast</td>
<td>194,280</td>
</tr>
<tr>
<td>Brain, Nervous System</td>
<td>22,070</td>
</tr>
<tr>
<td>Colorectal</td>
<td>146,970</td>
</tr>
<tr>
<td>Lung</td>
<td>219,440</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>74,490</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,550</td>
</tr>
<tr>
<td>Prostate</td>
<td>192,280</td>
</tr>
<tr>
<td>Skin</td>
<td>&gt;1,000,000</td>
</tr>
<tr>
<td>Urinary System</td>
<td>131,010</td>
</tr>
</tbody>
</table>

Table 12-1, p. 269
Age is a Leading Risk Factor for Cancer

![Graph showing the relationship between age and cancer deaths](image-url)

- **Cancer deaths (per 100,000)**
- **Age groups in years**
- **KEY**
  - Male
  - Female
Cancer and Genetics

- A predisposition to more than 50 forms of cancer are inherited to one degree or another (See Table 12.2)
- Most cancers are sporadic (not inherited)
- Most chemicals that cause cancer are mutagens
- Some viruses carry genes that promote cancer
- Specific chromosomal changes are found in certain cancers
- Mutations are the ultimate cause of cancer
12.2 Cancer Begins in a Single Cell

- A cell develops a mutation
- This cell accumulates specific mutations over a long period of time
- Cancer cell escapes control of the cell cycle and now can divide continuously
- Mutations continue to accumulate
- Cancer cells develop the ability to spread to other sites (metastatic)
- Cancer cells dedifferentiate – lose their specific abilities and acquire new ones
Second mutation

First mutation

Uncontrolled proliferation, cancer formation

Controlled growth; potential for cancer formation with a second mutation

Controlled growth, no cancer

Cell division over time
12.4 Genes involved in cancer

- **Tumor suppressor genes**
  - Cell cycle genes encoding proteins that suppress cell division
  - Deletion of the gene or inactivation of the protein can cause cells to divide continuously
  - *Retinoblastoma*

- **Proto-oncogenes**
  - Genes that initiate or maintain cell division
  - May become cancer genes (**oncogenes**) by mutation that renders them permanently on
  - *Ras* family genes
**G1/S Checkpoint Cell**
- Proceeds to S phase or enters inactive G0 state

**INTERPHASE**
- **G1** (Interval of cell growth before DNA replication; chromosomes unduplicated)
- **S** (Interval of cell growth when DNA replication is completed; chromosomes duplicated)

**CYTOKINESIS**
- Each daughter cell starts interphase

**MITOSIS (M)**
- Prophase
- Metaphase
- Anaphase
- Telophase
- Interphase ends for parent cell
- Interphase ends for daughter cell

**M Checkpoint Cell**
- Monitors attachment of spindle fibers to chromosomes

**G2/M Checkpoint Cell**
- Monitors completion of DNA synthesis and DNA damage

Fig. 12-5, p. 273
Many basic properties of cancer result from the inability of cancer cells to repair damage to DNA:

- High rates of mutation, chromosomal abnormalities, and genomic instability

DNA repair genes are now recognized as a class of cancer-related genes along with tumor suppressor genes and proto-oncogenes.

Breast cancer genes *BRCA1* and *BRCA2*
### Table 12.5  Human Genetic Disorders Associated with Chromosome Instability and Cancer Susceptibility

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Chromosome Damage</th>
<th>Cancer Susceptibility</th>
<th>Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia telangiectasia</td>
<td>Autosomal recessive</td>
<td>Translocations on 7, 14</td>
<td>Lymphoid, others</td>
<td>X-rays</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>Autosomal recessive</td>
<td>Breaks, translocations</td>
<td>Lymphoid, others</td>
<td>Sunlight</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>Autosomal recessive</td>
<td>Breaks, translocations</td>
<td>Leukemia</td>
<td>X-rays</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>Autosomal recessive</td>
<td>Breaks</td>
<td>Skin</td>
<td>Sunlight</td>
</tr>
</tbody>
</table>
Two-hit hypothesis

Proposed in 1953 by C.O. Nordling and then formalized by A. Knudson in 1971

- **sporadic**
  - normal
  - pre-cancer
  - cancer
  - tumor
  - mutation

- **inherited**
  - normal
  - pre-cancer
  - cancer
  - tumor
  - mutation
# Number of Mutations in Some Cancers

## Table 12.4  Number of Mutations Associated with Specific Forms of Cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Chromosomal Sites of Mutations</th>
<th>Minimal Number of Mutations Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoblastoma</td>
<td>13q14</td>
<td>2</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>11p13</td>
<td>2</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>5q, 12p, 17p, 18q</td>
<td>5 to 7</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>3p, 11p, 13q, 17p</td>
<td>10 to 15</td>
</tr>
</tbody>
</table>
Progression to cancer

- Cancer is a multistep process that usually requires six or more mutations required to initiate cancer.
1 Cancer cells break away from their original tissue.

2 The metastasizing cells become attached to the wall of a blood vessel or lymph vessel. They secrete digestive enzymes to create an opening. Then they cross the wall at the breach.

3 Cancer cells creep or tumble along inside blood vessels, then leave the bloodstream the same way they got in. They start new tumors in new tissues.
Other pathways to cancer (Not on exam)

- **Micro RNAs** (Chp9Pt2) normally control the expression of proto-oncogenes and tumor suppressor genes, when mutated, micro RNAs can change protein levels.

- **Telomerase** normal cells have telomerase turned off, limits cell division, but cancer cells must express telomerase to be able to divide indefinitely.

- **Chromosome translocations** move gene away from its promoter so that it is always being expressed or forms a new fusion protein that is capable of interfering with normal cell growth.

- **Epigenetic changes** to DNA (Chp9Pt2) usually involving abnormal histone methylation so that a gene stays on.

- **Viruses** – some viral proteins bind to and inactivate cell cycle checkpoint proteins, ultimately cell cycle cannot be stopped.
12.7 Hybrid Genes, Translocations, Genome Instability

- Changes in number and structure of chromosomes are common in cancer cells

Fig. 12-14, p. 280
# Translocations Associated with Cancers

## Table 12.6 Chromosomal Translocations Associated with Human Cancers

<table>
<thead>
<tr>
<th>Chromosomal Translocation</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(9;22)</td>
<td>Chronic myelogenous leukemia (Philadelphia chromosome)</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>Acute promyelocytic leukemia</td>
</tr>
<tr>
<td>t(11;19)</td>
<td>Acute monocytic leukemia, acute myelomonocytic leukemia</td>
</tr>
<tr>
<td>t(1;9)</td>
<td>Pre-B-cell leukemia</td>
</tr>
<tr>
<td>t(8;14),t(8;22),t(2;8)</td>
<td>Burkitt's lymphoma, acute lymphocytic leukemia of the B-cell type</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>Acute myelogenous leukemia, acute myeloblastic leukemia</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Chronic lymphocytic leukemia, diffuse lymphoma, multiple myeloma</td>
</tr>
<tr>
<td>t(4;18)</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>t(4;11)</td>
<td>Acute lymphocytic leukemia</td>
</tr>
<tr>
<td>t(11;14)(p13;q13)</td>
<td>Acute lymphocytic leukemia</td>
</tr>
</tbody>
</table>

Table 12-6, p. 281
Environmental and Lifestyle factors contribute to Cancer

- Sunlight and skin cancer
- Smoking: 85% of lung cancer in men and 75% in women are related to smoking
- Some viral infections lead to cancer: HPV and cervical cancer
- Radiation
- Occupational exposure to some chemicals poses a cancer risk to workers in a number of industries
Rates of melanoma diagnoses from 1973 - 2000

- Male and female
- Male
- Female

Year of diagnosis

Rate per 100,000

Fig. 12-20, p. 287
Wear sunscreen! And know what to watch for on your skin.

**Basal-cell carcinoma**
Slow-growing, benign

**Squamous-cell carcinoma**
Fast-growing, can be malignant

**Malignant melanoma**
Rapid growth, malignant, very dangerous
<table>
<thead>
<tr>
<th></th>
<th>ABCDEEs of Skin Cancer, ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><strong>Asymmetry</strong></td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><strong>Border</strong></td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><strong>Color</strong></td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><strong>Diameter</strong></td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><strong>Evolving</strong></td>
</tr>
</tbody>
</table>
12.8 Genomics and Cancer

- Sequencing cancer genomes has allowed the identification of additional cancer-associated genes.
Exploring Genetics: *The Cancer Genome Atlas*

- To employ large scale genome sequencing of cancer cells to catalog genetic changes and identify new genes
  - Brain cancer
  - Lung Cancer
  - Ovarian cancer

**Ultimately, this info allows researchers to target cancer therapies to specific genes and/or proteins**