Chapter 12
Genes and Cancer
Cancer

- Produced by the environment and the genotype
- Can affect many different cells and tissues in the body
- Results from unregulated cell proliferation
- May be able to metastasize or spread to other sites
Properties of cancer cells:

- Uncontrolled proliferation
- Ability to metastasize
- Are clonal

Tumors

- Malignant:
  - Invasive
  - Spread

- Benign:
  - Grow in place
  - Do not spread
### Table 18.2
**Characteristics of Cancer Cells**

- Oilier, less adherent
- Loss of cell cycle control
- Heritable
- Transplantable
- Dedifferentiated
- Lack contact inhibition
- Induce local blood vessel formation (angiogenesis)
- Invasive
- Increased mutation rate
- Can spread (metastasize)
Metastasis of Cancer Cells

(a) Cancer cells break away from their home tissue.

(b) The metastasizing cells become attached to the wall of a blood vessel or lymph vessel. They secrete digestive enzymes onto it. Then they cross the wall at the breach.

(c) 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.

Fig. 12.2
Unregulated Cell Cycle

- Cancer cells show uncontrolled cell division
- They have abnormal shapes
- Bypass checkpoints in the cell cycle

Fig. 12.4
The Cell Cycle
Checkpoint Genes

• **Tumor suppressor genes**
  – Suppress cell division
  – Act at either G1/S or G2/M control points

• **Proto-oncogenes**
  – Promote cell division if mutant

• **Oncogenes**
  – Mutant forms of proto-oncogenes induce or continue uncontrolled cell division
Cancer Is Most Often a Sporadic Event

- Cancer can be an inherited susceptibility or a sporadic event
- Sporadic cases are the most common
- In some inherited cancers, individuals carrying the mutant allele causing a predisposition to cancer have a 100,000 fold increased risk
Chapter 12

Human Heredity

by Michael Cummings ©2006 Brooks/Cole-Thomson Learning

p53 - ‘guardian of the genome’

DNA repair
Cancer Is a Genetic Disorder

Evidence that cancer has a genetic origin

- >50 forms of cancer have some degree of inherited predisposition
- Most carcinogens are also mutagens
- Some viruses carry mutant genes (oncogenes) that promote and maintain the growth of a tumor
- Specific chromosomal changes are found in some cancers
Cancer Begins with a Single Cell

• All cells in the tumor are descended from a single cell - **CLONAL**
• Most cancers develop after a cell accumulates multiple mutations over a long period of time
• Once formed, cancer cells divide continuously
• Mutations continue to accumulate and the cancer may become more aggressive
Lung cancer takes a long time to spread
Lung sections of non-smoker, left, and smoker, right.
## Inherited Susceptibilities

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Chromosome</th>
<th>OMIM Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset familial breast cancer</td>
<td>17q</td>
<td>113705</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>5q</td>
<td>175100</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>2p</td>
<td>120435</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>17p</td>
<td>151623</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td>11q</td>
<td>131100</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
<td>10</td>
<td>171400</td>
</tr>
<tr>
<td>Neurofibromatous type 1</td>
<td>17q</td>
<td>162200</td>
</tr>
<tr>
<td>Neurofibromatous type 2</td>
<td>22q</td>
<td>101000</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>13</td>
<td>180200</td>
</tr>
<tr>
<td>Von Hippel-Lindau disease</td>
<td>3p</td>
<td>193300</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>11p</td>
<td>194070</td>
</tr>
</tbody>
</table>
Cancer Is Caused by Mutations

- May be caused by a single dominant mutation or a number of recessive mutations in a somatic cell
- This causes uncontrolled cell growth
- Age is the leading risk factor for many cancers because cancer causing mutations accumulate over time
Several Independent Mutations May Cause Cancer

Fig. 12.3

Cell division over time

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Familial p53: Ly-Fraumeni Syndrome

One p53 mutant allele

- Cancer Risk
  - ~50% by age 30
  - ~90% by age 70
  - ~100% for Breast cancer
Retinoblastoma

- Cancer of the retina
- Diagnosed between 1–3 years of age
- 40% of all cases are due to an autosomal dominant trait
- 60% are sporadic cases

Fig. 12.6
Hereditary Retinoblastoma

- Autosomal dominant
- Individuals with the allele, $RB$ have a 90% chance of developing retinoblastoma
- Usually in both eyes
- High risk for other cancers especially osteosarcoma and fibrosarcoma

Fig. 12.7
Sporadic Form of Retinoblastoma

- Mutations occur in both copies of the \( RB1 \) gene at 13q14
- Tumors form generally in only one eye
- No increased risk of other cancers
Knudson Two-Step Model

- Disease develops when two mutant copies of *RB1* are present in the cell.
- With inherited retinoblastoma, a child inherits one mutant allele and if the normal copy becomes mutated, the child develops retinoblastoma.
- In the sporadic form, both copies must become mutated to develop the disease, generally only in one eye and later in childhood.
**RB1 gene**

- Located at 13q14 and encodes for protein pRB
- pRB regulates the cell cycle
  - It is present in most cells
  - Activated pRB prevents the cell from moving from G1 to S
- If both copies of the *RB1* gene are deleted or mutated, the cell divides in an uncontrolled manner

![Region containing retinoblastoma gene](image)
The Cell Cycle

- Prophase
- Metaphase
- Anaphase
- Telophase

G1

G2

S

RB

interphase

Fig. 12.5
Proto-Oncogenes to Oncogenes

• **Proto-oncogenes** turn cell division on or off
• Mutant forms permanently switch on cell division and are called **oncogenes**
• Many different types of mutations have been identified
• Example: *ras* proto-oncogene receives and transfers signal needed for cell division
Fig. 12.9

The diagram illustrates the role of the Ras oncogene in cancer development. It shows the normal ras gene and how mutations can lead to the production of mutant ras proteins, which result in different outcomes:

- Normal ras protein remains active, leading to no tumor formation.
- Mutant ras protein remains active, leading to tumor formation.
- Mutant ras protein becomes inactive, leading to tumor formation.

The diagram highlights the importance of gene regulation in the development of tumors.
Breast Cancer

- Most common form of cancer in US women, but also occurs in men
- 40,000 deaths/year
- Most cases are sporadic, but approximately 5% are the result of a mutation in the \textit{BRCA1} gene
- About 1/200 women inherit the allele; of these, approximately 90% will develop breast cancer
BRCA1 Gene

- Mary-Claire King’s research began in the 1970s
- In 1990, using recombinant DNA technology found linkage with a DNA marker
- Marker is also linked to ovarian cancer
- The autosomal dominant BRCA1 gene was identified in 1994
BRCA1 and BRCA2

- BRCA1 maps to chromosome 17
- Another autosomal dominant gene, BRCA2 maps to chromosome 13
- Together BRCA1 and BRCA2 account for 10–15% of genetic breast cancers
- Allele frequencies of these genes vary among populations
- Frequency of mutations high in Ashkenazi Jewish population
Some (depressing) facts about BRCA1 and BRCA2

Women with BRCA1 gene mutations have an 50% chance of developing breast cancer (compared to 13% in normal), and 16% chance of ovarian cancer by age 70 (compared to 1.6% in normal).

Also increased risk of prostate cancers in men. In men, estimated 1/6 men with a mutation will develop prostate cancer.

Note that just having the mutation does not automatically mean that breast cancer will develop, and vice versa.

73% of Ashkenazi Jews with family history of breast/ovarian cancer carry one of these mutations.

Different families have different mutations in BRCA1/2.

1% of the general Jewish population has mutations in BRCA1 and BRCA2. In general population, frequency is 0.1-0.6%.

Source: Genome.gov
**BRCA1 and BRCA2 Are DNA Repair Genes**

- Expression is highest at the G1/S boundary and S phase of the cell cycle
- BRCA proteins are activated when DNA is damaged
- Involved with repair of double stranded breaks in the DNA
- Regarded as tumor suppressor genes
Colon Cancer

- Common form of cancer, approximately 84% are sporadic forms
- Multiple mutations are required to initiate formation of cancer cell
- Two forms of genetic predisposition
  - Familial adenomatous polyposis (FAP) accounts for 1% of all cases
  - Hereditary nonpolyposis colon cancer (HNPCC) accounts for 15% of all cases
Colon and Rectal Cancer

<table>
<thead>
<tr>
<th>Table 12.2 Colon and Rectal Cancer in the United States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated new cases, 2004</strong></td>
</tr>
<tr>
<td>Colon</td>
</tr>
<tr>
<td>Rectum</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

**Mortality**
(estimated deaths, 2004)

Colon and rectum 56,730
(16% of cancer deaths)

**5-year survival rate**
(early detection)

Colon 90%
Rectum 85%
Familial Adenomatous Polyposis

- Autosomal dominant trait
- Mutation in the APC gene
- Frequency in general population 3/1,000
- Results in development of polyps and benign growths in the colon
- Polyps often become malignant

Fig. 12.11
Multistep model for Colon Cancer

![Multistep model for Colon Cancer diagram]

**Fig. 12.12**
Hereditary Nonpolyposis Colon Cancer

- Two forms
  - *HPNCC1* (2p16)
  - *HPNCC2* (3p23-21.3)
- Genes function to repair errors during DNA replication
- Mutations destabilize the genome, generating numerous mutations in DNA sequences known as microsatellites
- HNPCC tumors may carry more than 100,000 mutations
- Increased risk for many types of cancer
Mutations and 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>
Two Types of Genes Involved in Cancer

Gatekeeper genes

- Regulate cell growth and passage through cell cycle
  - Example tumor suppressor genes and some oncogenes

Caretaker genes

- Help maintain the integrity of the genome
  - Example DNA repair genes
## 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>
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</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>
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<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>
<tr>
<td>Chromosomal Translocation</td>
<td>Cancer</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>---------------------------</td>
<td>--------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(9;22)</td>
<td>Chronic myelogenous leukemia (Philadelphia chromosome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(15;17)</td>
<td>Acute promyelocytic leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;19)</td>
<td>Acute monocytic leukemia, acute myelomonocytic leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(1;9)</td>
<td>Pre-B-cell leukemia</td>
<td></td>
<td></td>
<td></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>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(8;21)</td>
<td>Acute myelogenous leukemia, acute myeloblastic leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Chronic lymphocytic leukemia, diffuse lymphoma, multiple myeloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4;18)</td>
<td>Follicular lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4;11)</td>
<td>Acute lymphocytic leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;14)(p13;q13)</td>
<td>Acute lymphocytic leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Philadelphia Chromosome

- Abnormal chromosome produced by a translocation between long arms of chromosome 9 and chromosome 22
- Linked to chronic myelogenous leukemia (CML)

Fig. 12.13
Translocations

• Chromosomal breaks can convert proto-oncogenes to oncogenes

• In CML
  – The oncogene \( c-abl \) is on chromosome 9 at the breakpoint; the \( bcr \) gene is on chromosome 22 at the breakpoint
  – Translocation creates a hybrid gene
  – The hybrid protein acts a signal for cell division causing CML
Chronic Myelogenous Leukemia

Fig. 12.15

Chromosome 22

\[ bcr \]

Chromosome 9

\[ c-abl \]

\( t(9;22) \)

Philadelphia chromosome

Hybrid \( bcr \) / \( c-abl \) gene

Hybrid Bcr-Abl protein

Uncontrolled cell growth

Chronic myelogenous leukemia (CML)
Myelogenous leukemia in human blood. LM X600.
Cancer Drugs

- Traditional chemo- and radiation therapy, target all rapidly dividing cells and create serious side effects
- New drug, Gleevec, targets the specific hybrid protein
- 90% of patients with early stage CML go into remission

Fig. 12.16
Avastin - prevents angiogenesis
does not cure, just prolongs life a bit

Herceptin - works on HER2 overexpressing metastatic breast cancer
May reduce the risk of relapse by 50%
Cancer and the Environment

- Epidemiological studies can identify variation in cancer deaths between populations and help identify environmental factors.

### Table 12.6 Age-Adjusted Cancer Death Rates per 100,000 Population

<table>
<thead>
<tr>
<th>Country</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>165.3 (27)*</td>
<td>111.1 (18)</td>
</tr>
<tr>
<td>Australia</td>
<td>158.5 (28)</td>
<td>100.2 (20)</td>
</tr>
<tr>
<td>Austria</td>
<td>171.6 (20)</td>
<td>105.6 (16)</td>
</tr>
<tr>
<td>Denmark</td>
<td>178.7 (17)</td>
<td>138.1 (1)</td>
</tr>
<tr>
<td>Germany</td>
<td>177.3 (18)</td>
<td>108.2 (11)</td>
</tr>
<tr>
<td>Hungary</td>
<td>258.7 (1)</td>
<td>135.2 (2)</td>
</tr>
<tr>
<td>Japan</td>
<td>149.8 (32)</td>
<td>75.2 (43)</td>
</tr>
<tr>
<td>Latvia</td>
<td>206.1 (6)</td>
<td>98.7 (23)</td>
</tr>
<tr>
<td>Mauritius</td>
<td>85.4 (47)</td>
<td>63.8 (46)</td>
</tr>
<tr>
<td>Mexico</td>
<td>81.6 (48)</td>
<td>77.6 (41)</td>
</tr>
<tr>
<td>Poland</td>
<td>204.2 (8)</td>
<td>107.6 (13)</td>
</tr>
<tr>
<td>Romania</td>
<td>140.2 (36)</td>
<td>84.5 (38)</td>
</tr>
<tr>
<td>Slovenia</td>
<td>203.9 (9)</td>
<td>108.0 (12)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>167.2 (24)</td>
<td>96.3 (26)</td>
</tr>
<tr>
<td>Trinidad, Tobago</td>
<td>120.0 (42)</td>
<td>91.4 (31)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>179.1 (16)</td>
<td>124.6 (5)</td>
</tr>
</tbody>
</table>

* Number in parentheses refers to rank order.
Human Genome and New Technologies

- Predict risk
- May help tailor diagnosis and treatment
- Development of specialized drugs
- Identify specific characteristics of cancer cells
Human papilloma virus infection can cause cervical cancer

Current recommendation: vaccinate using Gardasil - vaccine against HPV

Vaccine triggers antibody production against yeast-produced HPV proteins, protecting against future infection