Cancer
Cancer

OUTLINE:

- Uncontrolled Cell Division
- Development of Cancer
- Multiple Mutations
- Cancer Stem Cell Hypothesis
- Known Causes of Cancer
- Reducing the Risk of Cancer
- Diagnosing Cancer
- Treating Cancer
Uncontrolled Cell Division

- All forms of cancer share one characteristic: uncontrolled cell division
  - One in three people in U.S. will develop cancer
- Tumor (= neoplasm)
  - An abnormal growth of cells
- Two basic types
  - Benign
  - Malignant
Benign or Malignant Tumors

- **Benign tumor**
  - Abnormal mass of tissue surrounded by a capsule of connective tissue
  - Usually remains at the site where it forms
  - Often can be removed completely by surgery

- **Malignant tumor**
  - Invades surrounding tissue
  - Spreads to multiple locations (= metastasis)
  - Cancerous
Stages of Cancer Development

- Dysplasia in tissues of precancerous cells
- Carcinoma in situ
- Development of blood
- Metastasis
Stages of Cancer Development

- Dysplasia

- Precancerous cells look different from normal cells
  - Abnormal shape caused by ragged edges
  - Unusually large nuclei, with odd shape
    - May have extra chromosomes or be missing parts of some chromosomes
  - Form a disorganized clump
Figure 21a.1 Cancer cells have an abnormal appearance.
Figure 21a.2 A comparison of karyotypes.
Stages of Cancer Development

- Carcinoma *in situ* (“cancer in place”)
  - Tiny mass only a millimeter or two in diameter (about the size of a BB)

- Tumor attracts a blood supply
  - Blood brings nutrients and carries away wastes, allowing continued growth
  - Vessels form an escape route for tumor cells
  - As long as a tumor stays in place, it can grow quite large, and a surgeon would still be able to remove it (depending on the location)
**Stages of Cancer Development**

- **Metastasis**
  - Cancer cells leave original tumor and enter either the cardiovascular or lymphatic systems and travel to distant sites
    - Circulatory patterns often explain patterns of metastasis
    - Example: blood leaving the intestine travels to the liver, so colon cancer typically spreads to the liver
    - Once cancer cells leave the original tumor, they usually spread to so many locations that a surgeon’s scalpel is no longer an effective weapon
      - At this point, chemotherapy or radiation is generally used to kill the cancer cells wherever they are hiding
Figure 21a.3 The progression of cancer.

- **Initial tumor cell:** One cell acquires mutations, causing loss of control of cell division.
- **Cell divides more frequently than others.**
- **Carcinoma in situ:** Tumor remains at its site of origin.
- **Cells of the tumor release growth factors to attract a blood supply.**
- **Cells of malignant tumor:**
  - Attract a blood supply
  - Gain the ability to leave the other cells
  - Spread to distant sites (metastasize)
Development of Cancer

- The 30 to 50 trillion cells in the human body generally work cooperatively
  - There are controls that tell a cell when and how often to divide, when to self-destruct, and when to stay in place
  - Normal cells have a system of damage control
    - Detect, assess, and repair damage
    - If damage cannot be repaired, then initiate program of cell death
    - Tumor-suppressor genes important
  - Cancer cells escape the normal control mechanisms of healthy cells
Figure 21a.4 Steps in controlling DNA damage during the cell cycle.

1. **DNA damage detected**
2. **Damage control**
   - Stop cell division
   - Assess damage
   - Repair damage
3. **Repair is successful**
   - Cell returns to cell cycle
4. **Repair fails**
   - Damage accumulates, leading to cancer
5. **Damage too extensive for repair**
   - Programmed cell death
Development of Cancer

- Two types of genes regulate NORMAL cell division
  - Proto-oncogenes
    - Stimulate cell division
    - Example: ras
  - Tumor-suppressor genes
    - Inhibit cell division
    - Example: p53
- These genes regulate cell division, so that it normally occurs only for growth/repair
- Cancer cells lack restraints on cell division
Lack of Restraint on Cell Division

- Mutations in proto-oncogenes
  - Become oncogenes that speed rate of cell division (stuck accelerator of a car)
- Mutations in tumor-suppressor genes
  - Lead to uncontrolled cell division (no brakes in a car)
Lack of Restraint on Cell Division

- In tissue culture, normal cells exhibit contact inhibition
  - Divide until form a single layer of cells
  - Stop dividing when contact a neighbor
- Cancer cells do not show contact inhibition
  - Continue to divide, pile up and form a tumor
DNA Damage and Cell Destruction

- In normal cells, programmed cell death is initiated when genes regulating cell division have been damaged.
  - Also called apoptosis.
  - Condemned cells exhibit predictable series of physical changes, such as blebs.
DNA Damage and Cell Destruction

- Cancer cells do not self-destruct when their DNA is damaged
  - This makes them difficult to kill with radiation or chemotherapy
    - Treatments designed to damage DNA of cancer cells and trigger self-destruction
Figure 21a.5 Programmed cell death.
Development of Cancer

Cancer results when cells lose their ability to control cell division, which is often the result of mutations in proto-oncogenes and tumor-suppressor genes. This tutorial describes how the proteins coded for by these genes control the cell cycle and how malignant tumors may develop when these controls are lost.

Press "PLAY" to begin Animation.
Unlimited Cell Division

- In the lab, most normal human cells divide 50 to 60 times and then enter a nondividing state called senescence
  - Telomeres might be the way that a cell “counts” the number of times it has divided
    - Pieces of DNA at tips of chromosomes
    - Made by telomerase, early in development
    - Most mature cells stop producing telomerase
    - When DNA copied for cell division, tiny piece of every telomere in the cell is shaved off
Unlimited Cell Division

- Cancer cells do not stop producing telomerase
  - Telomeres are reconstructed after each cell division
    - May allow cell division to continue indefinitely
Figure 21a.6 *Telomeres.*

Telomeres are protective segments at the tips of chromosomes.
Blood Supply to Cancer Cells

- Cancer cells release special growth factors that cause capillaries to invade the tumor
  - Remove waste
  - Deliver nutrients
  - Deliver additional growth factors that spur tumor growth
  - Serve as routes by which cancer cells can leave tumor and spread to other locations
Adherence to Neighboring Cells

- Normal cells
  - Usually “glued” in place by cell adhesion molecules (CAMs)
  - If become “unglued,” stop dividing and self-destruct

- Cancer cells
  - Secrete enzymes that break down CAMs, so they are able to break free
  - Continue to divide and evade self-destruction
    - Oncogenes send false message to nucleus saying that the cell is attached
Body Defense Cells

- Natural killer cells and cytotoxic T cells usually kill cancer cells that develop in our bodies every day
  - Some types of cancer cells actively inhibit these defense cells
  - Others multiply too quickly for defense cells to destroy them all
- Healthy cells have interacting control systems that usually prevent development of cancer
Table 21a.1 Review of Control Mechanisms That Fail in Cancer

<table>
<thead>
<tr>
<th>Mechanisms That Protect Cells from Cancer</th>
<th>Method of Evasion Used by Cancer Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genetic controls on cell division</strong></td>
<td></td>
</tr>
<tr>
<td>Proto-oncogenes stimulate cell division through effects on growth factors and certain other cell-signaling mechanisms</td>
<td>Oncogenes promote cell division</td>
</tr>
<tr>
<td>Tumor-suppressor genes inhibit cell division</td>
<td>Mutations in tumor-suppressor genes take the “brakes” off cell division</td>
</tr>
<tr>
<td><strong>Programmed cell death</strong></td>
<td></td>
</tr>
<tr>
<td>A genetic program that initiates events that lead to the death of the cell when damaged DNA is detected or another signal is received</td>
<td>Mutations in tumor-suppressor genes: Mutant gene p53 no longer triggers cell death when damaged DNA is detected</td>
</tr>
<tr>
<td><strong>Limitations on the number of times a cell can divide</strong></td>
<td></td>
</tr>
<tr>
<td>Telomeres protect the ends of chromosomes, but a fraction of each is shaved off each time the DNA is copied; when the telomeres are gone, the chromosome tips can stick together, causing the cell to die</td>
<td>Genes to produce telomerase, the enzyme that reconstructs telomeres, are turned on in cancer cells so telomere length is stabilized</td>
</tr>
<tr>
<td><strong>Controls that prevent the formation of new blood vessels</strong></td>
<td></td>
</tr>
<tr>
<td>These controls are normally in effect except in a few instances, such as wound healing</td>
<td>Cancer cells produce growth factors that attract new blood vessels and proteins that counter the normal proteins that inhibit blood vessel formation</td>
</tr>
<tr>
<td><strong>Controls that keep normal cells in place</strong></td>
<td></td>
</tr>
<tr>
<td>Cellular adhesion molecules (CAMs) hold cells in place; unanchored cells stop dividing and self-destruct</td>
<td>Cancer cells’ oncogenes send a false message to the nucleus that the cell is properly anchored</td>
</tr>
</tbody>
</table>
Multiple Mutations

- Development of cancer is a multistep process involving multiple mutations and changes in gene activity
  - Each mutation brings a cell closer to becoming cancerous
  - Damage must occur in at least two genes (and typically more than six genes) before cancer occurs
Figure 21a.7 Multiple mutations must occur.
Figure 21a.8 Steps in colon cancer.

1. Normal colon epithelial cells
2. Mutation in tumor-suppressor gene
3. Mutation forms oncogene
4. Small benign growth called a polyp
5. Larger polyp
6. Mutation in tumor-suppressor gene
7. Malignant tumor
8. Additional mutations
9. Cancer cells spread
10. Additional mutations
Cancer Stem Cell Hypothesis

- All cells of a cancerous tumor are genetically identical.
  - Descendants of a single cell that accumulated the mutations necessary for it to lose control over cell division.

- However, only some cells within the tumor are capable of continually dividing.
  - Called cancer stem cells.
    - Have surface markers that differ from those of other tumor cells.
Known Causes of Cancer

- Genetic changes that turn normal cells into cancer cells are usually brought about by:
  - Viruses
  - Mutations caused by exposure to certain chemicals or radiation
Known Causes of Cancer

- Viruses
  - Cause about 5% of cancers in the U.S.
    - Viruses may have oncogenes among their genes, which enter the host cell
    - Viral DNA may be inserted into host DNA at a site that disrupts the functioning of a gene that regulates cell division in host
    - Viruses may interfere with immune system
**Table 21a.2 Some Viruses Linked to Human Cancer**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Types of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human papillomaviruses (HPVs)</td>
<td>Cervical, penile, and other anogenital cancers in men and women</td>
</tr>
<tr>
<td>Hepatitis B and C viruses</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>B cell lymphomas, especially Burkitt’s lymphoma; nasopharyngeal carcinoma</td>
</tr>
<tr>
<td>Human T cell leukemia virus (HTLV-1)</td>
<td>Adult T cell leukemia</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Lymphomas and leukemias</td>
</tr>
<tr>
<td>Kaposi sarcoma– herpesvirus</td>
<td>Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>

© 2014 Pearson Education, Inc.
Chemicals

- Carcinogens are environmental agents that foster the development of cancer
  - Chemical carcinogens
    - May cause mutations in genes that regulate cell division
      - Chemicals in tobacco smoke
      - Alcohol in excess
      - Formaldehyde, benzene, certain pesticides
    - May stimulate cell division
      - Estrogen stimulates cell division in breast and endometrial tissues
        - Can cause cancer to progress
Radiation

- Causes mutations in DNA that can lead to cancer
- Includes cosmic rays, radon, uranium, and UV light from sun
Reducing the Risk of Cancer

- Cancer is a family of more than 200 diseases
  - Usually named for organ in which tumor arises
    - Carcinomas (epithelial tissues)
    - Leukemias (bone marrow)
    - Sarcomas (muscle, bone, cartilage)
    - Lymphomas (lymphatic tissue)
Reducing the Risk of Cancer

- Second leading cause of death in industrialized countries
  - Tobacco use and unhealthy diet account for two-thirds of all cancer deaths in the United States
- Certain lifestyle habits greatly reduce the risk of developing cancer
Figure 21a.9 2012 estimates for the leading types of cancer in terms of new cases and deaths.

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated New Cases</strong></td>
<td><strong>Estimated Deaths</strong></td>
<td><strong>Estimated New Cases</strong></td>
<td><strong>Estimated Deaths</strong></td>
</tr>
<tr>
<td>Prostate</td>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>241,740 (29%)</td>
<td>87,750 (29%)</td>
<td>28,170 (9%)</td>
<td>72,590 (26%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Prostate</td>
<td>Colon &amp; rectum</td>
<td>Breast</td>
</tr>
<tr>
<td>116,470 (14%)</td>
<td>109,690 (14%)</td>
<td>70,040 (9%)</td>
<td>39,510 (14%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>73,420 (9%)</td>
<td>26,470 (9%)</td>
<td>25,220 (9%)</td>
<td>25,220 (9%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Pancreas</td>
<td>Pancreas</td>
<td>Pancreas</td>
</tr>
<tr>
<td>55,600 (7%)</td>
<td>18,850 (6%)</td>
<td>18,540 (7%)</td>
<td>18,540 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Liver &amp; intrahepatic bile duct</td>
<td>Leukemia</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>44,250 (5%)</td>
<td>13,980 (5%)</td>
<td>15,500 (6%)</td>
<td>15,500 (6%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Leukemia</td>
<td>Leukemia</td>
<td>Leukemia</td>
</tr>
<tr>
<td>40,250 (5%)</td>
<td>13,500 (4%)</td>
<td>10,040 (4%)</td>
<td>10,040 (4%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Esophagus</td>
<td>Non-Hodgkin lymphoma</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>38,160 (4%)</td>
<td>12,040 (4%)</td>
<td>8,620 (3%)</td>
<td>8,620 (3%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Urinary bladder</td>
<td>Uterine corpus</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>28,540 (3%)</td>
<td>10,510 (3%)</td>
<td>8,010 (3%)</td>
<td>8,010 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Non-Hodgkin lymphoma</td>
<td>Liver &amp; intrahepatic bile duct</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>26,830 (3%)</td>
<td>10,320 (3%)</td>
<td>6,570 (2%)</td>
<td>6,570 (2%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Kidney &amp; renal pelvis</td>
<td>Brain &amp; other nervous system</td>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td>22,090 (3%)</td>
<td>8,650 (3%)</td>
<td>5,980 (2%)</td>
<td>5,980 (2%)</td>
</tr>
<tr>
<td>All other sites</td>
<td>All other sites</td>
<td>All other sites</td>
<td>All other sites</td>
</tr>
<tr>
<td>160,820 (18%)</td>
<td>161,200 (20%)</td>
<td>71,580 (25%)</td>
<td>64,790 (24%)</td>
</tr>
</tbody>
</table>

© 2014 Pearson Education, Inc.
Table 21a.4 Tips for Reducing Your Cancer Risk

<table>
<thead>
<tr>
<th>TABLE 21a.4 Tips for Reducing Your Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do not use tobacco. If you do, quit. Avoid exposure to secondhand smoke.</td>
</tr>
<tr>
<td>2. Reduce the amount of saturated fat in your diet, especially the fat from red meat.</td>
</tr>
<tr>
<td>3. Minimize your consumption of salt-cured, pickled, and smoked foods.</td>
</tr>
<tr>
<td>4. Eat at least five servings of fruit and vegetables every day.</td>
</tr>
<tr>
<td>5. Avoid excessive alcohol intake. If you consume alcohol, one or two drinks a day should be the maximum.</td>
</tr>
<tr>
<td>6. Watch your caloric intake, and maintain a healthy body weight.</td>
</tr>
<tr>
<td>7. Avoid excessive exposure to sunlight. Wear protective clothing. Use sunscreen.</td>
</tr>
<tr>
<td>8. Avoid unnecessary medical x-rays.</td>
</tr>
<tr>
<td>9. Have the appropriate screening exams on a regular basis. Women should have PAP tests and mammograms. Men should have prostate tests. All adults should have tests for colorectal cancer.</td>
</tr>
</tbody>
</table>
Diagnosing Cancer

- Early detection is critical to cancer survival
  - Successful treatment is much more likely before the cancer has spread
- Methods of detection
  - Self-examination
  - Medical screening and tests
    - Routine screening
    - Imaging
  - Biopsy
  - Tumor marker tests
  - Genetic tests
Diagnosing Cancer

- Cancer’s seven warning signs (American Cancer Society)
  - Change in bowel or bladder function
  - A sore throat that does not heal
  - Unusual bleeding or bloody discharge
  - Thickening or lump in breast or elsewhere
  - Indigestion or difficulty swallowing
  - Obvious change in wart or mole
  - Nagging cough or hoarseness
Figure 21a.10 Imaging techniques such as x-rays or MRIs can detect tumors.

(a) Mammogram of a breast cancer tumor (white area)

(b) MRI of a cancerous brain tumor (bright purple area)
### Table 21a.5 Recommended Cancer Screening Tests

#### Guidelines suggested by the American Cancer Society for the early detection of cancer in people without symptoms, age 20 to 40

**Cancer-related checkup every 3 years**

Should include the procedures listed below plus health counselling (such as tips on quitting cigarette smoking) and examinations for cancers of the thyroid, testes, prostate, mouth, ovaries, skin, and lymph nodes. Some people are at higher than normal risk for certain cancers and may need to have tests more frequently.

#### Breast cancer
- Exam by doctor every 3 years
- Self-exam every month
- One baseline breast x-ray ages 35 to 40

Higher risk for breast cancer: Personal or family history of breast cancer; never had children; had first child after 30

#### Uterine cancer
- Women should report any vaginal bleeding or discharge to their doctors

#### Cervical cancer
- Yearly PAP test beginning at age 21 or 3 years after sexual activity begins

Higher risk for cervical cancer: Early age at first intercourse; multiple sex partners

#### Guidelines suggested by the American Cancer Society for the early detection of cancer in people without symptoms, age 40 and over

**Cancer-related checkup every year**

Should include the procedures listed below plus health counselling (such as tips on quitting cigarette smoking) and examinations for cancers of the thyroid, testes, prostate, mouth, ovaries, skin, and lymph nodes. Some people are at higher than normal risk for certain cancers and may need to have tests more frequently.

#### Colon and rectal cancer
- Fecal occult blood test every year after age 50
- Flexible sigmoidoscopy beginning at age 50 and every 5 years thereafter, or colonoscopy every 10 years

Higher risk for colorectal cancer: Personal or family history of colon or rectal cancer; personal or family history of polyps in the colon or rectum; ulcerative colitis

#### Breast cancer
- Exam by doctor every 3 years
- Self-exam every month
- Breast x-ray every year after 40

Higher risk for breast cancer: Personal or family history of breast cancer; never had children; had first child after 30

#### Uterine cancer
- Pelvic exam every year

#### Cervical cancer
- Yearly PAP test

Higher risk for cervical cancer: Early age at first intercourse; multiple sex partners

#### Endometrial cancer
- Endometrial tissue sample at menopause if at risk

Higher risk of endometrial cancer: Infertility, obesity, failure of ovulation, abnormal uterine bleeding, estrogen therapy

#### Prostate cancer
- Yearly prostate-specific antigen (PSA) blood test and digital rectal exam after age 50
Treating Cancer

- Mainstays
  - Surgery
  - Radiation therapy
  - Chemotherapy

- Some newer treatments
  - Immunotherapy
  - Inhibition of blood vessel formation
  - Gene therapy
Surgery

- Performed when tumor is accessible and can be removed without damaging vital tissue
- Complete cure possible with early tumors (carcinoma in situ)
- If cancer has spread, then other forms of treatment necessary
Radiation

- Used when cancer has spread from initial site but is still localized
- Typically follows surgery
Radiation

- Radiation damages DNA and extensive damage triggers programmed cell death
  - Greatest damage done to rapidly dividing cells, which include
    - Cancer cells
    - Normal cells of renewal tissues
  - Destruction of renewal tissues causes side effects of radiation, such as temporary sterility, nausea, anemia, and hair loss
Chemotherapy

- Used when cancer has spread at diagnosis
- Drugs carried by the circulatory system
- Used to kill rapidly dividing cells throughout the body
  - Side effects similar to those for radiation
- Actions of drugs
  - Block DNA synthesis
  - Damage DNA
  - Prevent cell division
Radiation and Chemotherapy

- Goal: damage DNA in rapidly dividing cells, which should prompt the cells to self-destruct

- Problem: \textit{p53} gene (detects DNA damage and initiates programmed cell death) is mutant in more than half of all cancers
  - Thus, although treatment may damage DNA in cancer cells, the cells do not self-destruct, so treatment fails
Immunotherapy

- Cytotoxic T cells of the immune system continually search for abnormal cells, including cancer cells, and destroy them.

- Goal: boost the natural immune responses against cancer cells.
  - Two types of vaccines:
    - Vaccines against viruses that cause cancer: human papillomaviruses that cause cervical cancer.
    - Vaccines that stimulate T cells to attack and kill cancer cells:
      - Do not prevent disease; treat disease.
      - In clinical trials.

© 2014 Pearson Education, Inc.
Gene Therapy

- Numerous clinical trials using gene therapy to treat cancer are underway

- Treatment strategies
  - Insert normal tumor-suppressor genes into cancerous cells
  - Insert into a cancer cell a piece of DNA that prevents an oncogene from being effective
  - Insert a gene into tumor cells that will make them more sensitive to a drug that will kill them
Gene Therapy

abc NEWS | Gene Therapy and Cancer
You Should Now Be Able To:

- Understand what is uncontrolled cell division
- Know the steps in cancer development
- Define the multiple mutations that take place
- Know the cancer stem cell hypothesis
- Understand the known causes of cancer
- Know how to reduce the risk of cancer
- Know the methods used to diagnose cancer
- Know the possible treatments available