Biology, Clinical Manifestations, and Treatment of Cancer

Cancer Epidemiology

Cancer

- Derived from Greek word for crab, *karkinoma*
- Malignant tumor
- Tumor
  - Also referred to as a __________ — new growth

Benign vs. Malignant Tumors

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
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</table>
| Grow slowly | Can spread distantly (
| Well-defined capsule | |
| Not invasive | |
| Well differentiated | |
| Low mitotic index | |
| Do not metastasize | |

Mitotic index = rate of growth

Classification and Nomenclature

- Benign tumors
  - Named according to the tissues from which they arise, and include the suffix “-oma”
    - Lipoma
    - Hemangioma
    - Leiomyoma
    - Chondroma

- Malignant tumors
  - Named according to the tissues from which they arise
  - Malignant epithelial tumors are referred to as *carcinomas*
    - Adenocarcinoma (from ________ epithelium)
  - Malignant CT tumors are referred to as *sarcomas*
    - Rhabdomyosarcomas (from skeletal muscle)

Classification and Nomenclature

- Cancers of lymphatic tissue are *lymphomas*
- Cancers of blood-forming cells are *leukemias*
- Carcinoma in situ (*CIS*)
  - Epithelial malignant tumors that have not broken through BM or invaded the surrounding stroma
Classification and Nomenclature

Stages of Cancer Spread

- Stage 1: Confined to organ of origin
- Stage 2: Locally invasive
- Stage 3: Spread to lymph nodes
- Stage 4: Spread to distant sites
- CIS special case

Tumor Staging by TNM System

Tumor Markers

- Tumor cell markers (biologic markers) are substances produced by cancer cells or that are found on plasma cell membranes, in the blood, CSF, or urine
  - Hormones (Epi – in blood, adrenal medullary tumor)
  - Enzymes
  - Genes
  - Antigens (PSA – in blood, prostate cancer)
  - Antibodies

Hallmarks of Cancer

Viruses and Cancer

- Implicated
  - Hepatitis B and C viruses
  - Epstein-Barr virus (EBV)
  - Kaposi’s sarcoma herpesvirus (KSHV)
  - Human papillomavirus (HPV)
  - Human T cell leukemia–lymphoma virus (HTLV)
**Bacterial Cause of Cancer**

- *Helicobacter pylori*
  - Chronic infections are associated with:
    - Peptic ulcer disease
    - Stomach carcinoma
    - Mucosa-associated lymphoid tissue lymphomas

**Inflammation and Cancer**

- Chronic __________ is an important factor in development of cancer
  - Cytokine release from inflammatory cells
  - Free radicals
  - Mutation promotion
  - Decreased response to DNA damage

**Tumor Spread**

- Direct invasion of contiguous organs
  - Known as local spread

- Metastases to distant organs
  - Lymphatics and blood

- Metastases by way of implantation

**Local Spread**

- Invasion
  - Cellular multiplication
    - Mitotic rate vs. cellular death rate
  - Mechanical pressure
  - Release of lytic enzymes
  - Decreased cell-to-cell adhesion
  - Increased motility
    - Intravasation
    - Extravasation

**Three-Step Theory of Invasion**

- Tumor cell attachment
  - Fibronectin and laminin

- Degradation or dissolution of the matrix
  - Enzymes

- Locomotion into the matrix
  - Invadopodia (pseudopodia)

**HeLa cell**

- A cell type in an immortal cell line used in research
- One of the oldest, most commonly used human cell lines
- Derived from cervical cancer cells taken from Henrietta Lacks
- Patient eventually died of her cancer on October 4, 1951
- Cell line was found to be remarkably durable
- Cells propagated by George Otto Gey
- First human cell line to prove successful in vitro, which was a scientific achievement for the benefit of science
- Neither Lacks nor her family gave Gey permission
  - At that time, permission was neither required nor sought
- HeLa cells were used by Jonas Salk to test the first polio vaccine in the 1950's
Concept Check

1. Neoplasia  a. abnormal proliferating cells w/ higher degree of autonomy
2. Anaplasia  b. lack of differentiation, primitive cells
3. Autonomy  c. cancer cells' independence from normal cell controls
4. Tumor markers  d. substances produced by cancer cells

5. Which characterizes cancer cells?
   - A. Poorly differentiated
   - B. Metastasis
   - C. Infiltrative growth
   - D. Poor cell cohesiveness
   - E. All of the above

6. Which is/are not malignant?
   - A. Glioma
   - B. Adenocarcinoma
   - C. Rhabdomyoma
   - D. Leukemia
   - E. A and C

7. Metastasis is:
   - A. Alteration in normal cell growth
   - B. Growth of benign or malignant cells
   - C. Mutational
   - D. Ability to establish a secondary neoplasm at a new site

8. CIS is:
   - A. Preinvasive
   - B. Glandular or epithelial lesion
   - C. Teratoma
   - D. Carcinoma that has broken through BM
   - E. Both a and b are correct

Cancer Epidemiology

Chapter 10

Environmental Risk Factors

<table>
<thead>
<tr>
<th>Increased</th>
<th>Decreased</th>
</tr>
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<tbody>
<tr>
<td>Tobacco</td>
<td>Exercise</td>
</tr>
<tr>
<td>Radiation</td>
<td>Proper Diet</td>
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<tr>
<td>Alcohol</td>
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<td>Sexual Behavior</td>
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<tr>
<td>Diet</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Occupational Hazards</td>
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<tr>
<td>Electromagnetic Fields</td>
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</table>

- Tobacco
  - Multipotent carcinogenic mixture
  - Linked to cancers of the lung, lower urinary tract, aerodigestive tract, liver, kidney, pancreas, cervix
  - Linked to myeloid leukemia
Environmental Risk Factors

- Ionizing radiation
  - Emission from x-rays, radioisotopes, and other radioactive sources
  - Exposure causes cell death, gene mutations, and chromosome aberrations
  - Bystander effects
  - Poor gene repair
  - Changes in gap junction intercellular communication

- Ultraviolet radiation
  - Causes ____________ carcinoma, ____________ carcinoma, and melanoma
  - Principal source is ____________
  - Ultraviolet A (UVA) and ultraviolet B (UVB)
  - Promotes skin inflammation and release of free radicals

- Alcohol consumption
  - Risk factor for oral cavity, pharynx, hypopharynx, larynx, esophagus, and liver cancers
  - Cigarette/alcohol combination increases a person's risk

- Sexual reproductive behavior
  - Carcinogenic types of human papilloma virus
  - High-risk HPV

- Physical activity
  - Reduces cancer risk
    - Decreases insulin and insulin-like growth factors
    - Decreases obesity
    - Decreases inflammatory mediators and free radicals
    - Increased gut motility

- Occupational hazards
  - Substantial number of occupational carcinogenic agents
    - Asbestos
    - Dyes, rubber, paint, explosives, rubber cement, heavy metals, air pollution, etc.
    - Radon
Environmental Risk Factors

- Electromagnetic fields
  - Carcinogenic?
  - Are they, or aren’t they?

- Diet
  - Xenobiotics
    • Toxic, mutagenic, and carcinogenic chemicals in food
    • Activated by phase I activation enzymes
    • Defense mechanisms
      - Phase II detoxification enzymes
    • Examples
      - Compounds produced in the cooking of fat, meat, or proteins
      - Alkaloids or mold by-products

- Obesity
  - Correlates with the body mass index (BMI)
  - Adipose tissue is active endocrine and metabolic tissue
  - In response to endocrine and metabolic signaling, adipose tissue releases free fatty acids
    • Increased free fatty acids gives rise to insulin resistance and causes chronic hyperinsulinemia
    • Correlates with colon, breast, pancreatic, and endometrial cancers

Clinical Manifestations of Cancer

- Pain
  - Little or no pain is associated with early stages of malignancy
  - Influenced by fear, anxiety, sleep loss, fatigue, and overall physical deterioration
  - Mechanisms
    • Pressure, obstruction, invasion of sensitive structures, stretching of visceral surfaces, tissue destruction, and inflammation

- Fatigue
  - Subjective clinical manifestation
  - Tiredness, weakness, lack of energy, exhaustion, lethargy, inability to concentrate, depression, sleepiness, boredom, and lack of motivation
  - Suggested causes
    • Sleep disturbance, biochemical changes (cytokines), secondary to disease and treatment, psychosocial factors, level of activity, nutritional status, and environmental factors
Clinical Manifestations of Cancer

- Syndrome of cachexia (Gr. “_________”)
  - Most severe form of _________________
  - Present in 80% of cancer patients at death
  - Includes:
    - Anorexia, early satiety, weight loss, anemia, asthenia, taste alterations, and altered protein, lipid, and CHO metabolism

Cachexia

Clinical Manifestations of Cancer

- Anemia
  - A decrease of ______________ in the blood
  - Mechanisms
    - Chronic bleeding resulting in iron deficiency, severe malnutrition, medical therapies, or malignancy in blood-forming organs

Clinical Manifestations of Cancer

- Leukopenia and thrombocytopenia
  - Direct tumor invasion to the bone marrow causes leukopenia and thrombocytopenia
  - Chemotherapy drugs are toxic to the bone marrow
  - Infection
    - Risk increases when the absolute neutrophil and lymphocyte counts fall

Clinical Manifestations of Cancer

- Infection
  - Risk increases when the absolute neutrophil and lymphocyte counts fall

Cancer Treatment

- Chemotherapy
  - Use of nonselective cytotoxic drugs that target vital cellular machinery or metabolic pathways critical to both malignant and normal cell growth and replication
  - Goal
    - Eliminate enough tumor cells so body’s defense can eradicate any remaining cells

Cancer Treatment

- Chemosensitivity
  - Compartment
  1: cells undergoing mitosis and cytokinesis
  2: cells capable of entering the cell cycle in G1 phase
  3: cells not dividing or have irreversibly left cell cycle
  - Cells in compartment 3 will die a natural death
Cancer Treatment

- Ionizing radiation
  - Eradicate cancer without excessive toxicity
    - Avoid damage to normal structures
  - Ionizing radiation damages the cancer cell’s DNA
- Surgery
  - Biopsy and lymph node sampling
    - Sentinel nodes
  - Debulking surgery—remove most of tumor
  - Palliative surgery—relief of symptoms
- Hormone therapy
  - Receptor activation or blockage
  - Interferes with cellular growth and signaling

Immunotherapy

- Theoretically, antitumor responses can selectively eliminate cancer cells while sparing normal cells
- Immune memory is long lived
- Numerous immunologic mechanisms are capable of rejecting different types of cancer
- Biologic response modifiers (BRMs)

Other forms of immunotherapy

- Interferon administration
- Antigens
- Effector cell lymphokines
- Monoclonal antibodies

Side Effects of Cancer Treatment

- Gastrointestinal tract
- Bone marrow
- Hair and skin
- Reproductive tract

Concept Check

1. Likely cause for fatigue in cancer patients:
   - A. Biochemical changes due to treatment
   - B. Muscle loss
   - C. Psychologic factors
   - D. All of the above

2. The pain experience with cancer:
   - A. Affects the patient only in the early stages
   - B. Occurs in bone metastasis
   - C. Due to tissue necrosis
   - D. Both b and c are correct