Recap

Cancer Epidemiology

• Major insights into the causes of cancer can be obtained by epidemiologic studies
• Relate particular environmental, racial (possibly hereditary), and cultural influences to the occurrence of specific neoplasms
Cancer Incidence/Mortality

- Second leading cause of death in the US
- Death rates for specific cancers have changed over past few decades
  - Increase in lung cancer in females
  - Decrease in gastric carcinoma in U.S.
- Global issue

Cancer statistics, 2015

Variables

- Geography
- Environmental
- Age
- Race
- Acquired predisposing conditions
- Genetic predisposition
- Genetic + Inherited factors
Geography

Geographic variation in incidence thought to stem from differences in exposure to environmental carcinogens

- Death rate for stomach carcinoma in men and women is about seven times higher in Japan than in the United States.
- Liver cell carcinoma is relatively infrequent in the United States but is the most lethal cancer among many African populations.
- Nearly all the evidence indicates that these geographic differences are environmental rather than genetic in origin.

Geography

Nisei (second-generation Japanese living in the United States) have mortality rates for certain forms of cancer that are intermediate between those in natives of Japan and in Americans who have lived in the United States for many generations.

The two rates come closer with each passing generation.

Variables

- Geography
- Environmental
- Age
- Race
- Acquired predisposing conditions
- Genetic predisposition
- Genetic + Inherited factors
Environmental Variables

- Carcinogens
  - Agents that damage DNA increasing risk for cancer
- Tobacco:
  - Major cause of preventable deaths in US
  - LUNG, upper airway, bladder, pancreas, kidney, and esophagus
- Alcohol
  - Oral cavity, pharynx, larynx, esophagus, liver (secondary to cirrhosis)

Environmental Variables

- OBESITY
  - US epidemic
    - Spreading to other parts of world
  - Clearest associations with obesity
    - Esophagus
    - Pancreas
    - Colon/rectum
    - Breast
    - Kidney
    - Thyroid
    - Bladder

  Proposed mechanisms??
  - Elevated insulin levels
  - Increased estrogens
  - Decreased adiponectin
  - Proinflammatory state

Environmental Variables

- Occupational Exposures
  - Polycyclic hydrocarbons in coal products, tar, mineral oils, car exhaust
    - Lung cancer
  - Aromatic amines and azo dyes in dye and rubber industry; as food colors
    - Bladder cancer
  - Asbestos exposure in construction, ship building
    - Mesothelioma, lung cancer
- Sunlight
- Radiation
- Sexual exposures
There is no escape: it seems that everything people do to earn a livelihood, to subsist, or to enjoy life turns out to be illegal, immoral, or fattening, or—most disturbing—possibly carcinogenic.

ROBBINS PATHOLOGY

Variables

• Geography
• Environmental
• Age
• Race
• Acquired predisposing conditions
• Genetic predisposition
• Genetic + Inherited factors

Age

• In general frequency of cancer increases with age
  – Rising accumulation of somatic mutations
  – Decline in immune competence
• Most cancers in >55 years old
• Rate declines >75 years of age
• Cancer accounts for slightly >10% of deaths in children <15 y old
  – Leukemias, CNS neoplasms most common
Heredity

- Most cancers sporadic, some are familial
- Three main categories based on pattern of inheritance
  - Autosomal Dominant Cancer Syndromes
  - Autosomal Recessive Syndromes of Defective DNA Repair
  - Familial Cancers of Uncertain Inheritance

Autosomal Dominant Cancer Syndromes
- Inheritance of a single mutant gene greatly increases risk of developing a tumor

Examples
Familial adenomatous polyps of colon
- Nearly 100% develop colon cancer

Familial retinoblastoma
- 100,000 times risk of cancer than in general population
Autosomal Recessive Syndromes of Defective DNA Repair
- A group of rare autosomal recessive disorders
- Collectively characterized by chromosomal or DNA instability and high rates of certain cancers.
- One of the best-studied is xeroderma pigmentosum, in which DNA repair is defective.

Familial Cancers of Uncertain Inheritance
- Virtually all the common types of cancers that occur sporadically have been reported to occur in familial forms
- Pattern of inheritance is unclear
- For example: carcinomas of colon, breast, ovary, and brain.

Features that characterize familial cancers include early age at onset, tumors arising in two or more close relatives of the index case, and sometimes multiple or bilateral tumors.

Acquired Predisposing Conditions
- Preneoplastic lesions
- Chronic inflammation/Chronic tissue injury
  - Smoking – squamous metaplasia – dysplasia (bronchial mucosa)
  - Unopposed estrogen – endometrial hyperplasia and dysplasia
SUMMARY - Epidemiology of Cancer

- The incidence of cancer varies with age, race, geographic factors, and genetic backgrounds.
- Cancers are most common at the two extremes of age.
- The geographic variation results mostly from different environmental exposures.
- Most cancers are sporadic, but some are familial.
- Predisposition to hereditary cancers may be autosomal dominant or autosomal recessive. The former usually are linked to inheritance of a germ line mutation of cancer suppressor genes, whereas the latter typically are associated with inherited defects in DNA repair.
- Familial cancers tend to be bilateral and arise earlier in life than their sporadic counterparts.
- Some acquired diseases, known as preneoplastic disorders, are known to be associated with an increased risk for development of cancer.

CARCINOGENESIS
Molecular Basis of Cancer

Fundamental principles
- Cancer is a genetic disorder caused by DNA mutations
- Most mutations spontaneous or induced by environmental insults
- Some mutations are inherited in the germ line
- Cancer arises from clonal expansion of a single progenitor cell that has incurred damage (monoclonal)
- Four classes of normal regulatory genes are key targets of cell damage
Target Regulatory Genes

- Growth promoting proto-oncogenes
- Growth inhibiting tumor suppressor genes
- Genes that regulate apoptosis
- Genes involved in DNA repair

Collectively, the genetic alterations in tumor cells confer growth and survival advantages over normal cells.

Proto-Oncogenes & Oncogenes

- Proto-oncogenes
  - Normal cellular genes whose products promote cell proliferation
- Oncogenes
  - Mutant or over-expressed versions of normal proto-oncogenes
  - Function autonomously
  - Encode transcription factors, growth regulating proteins, cell survival proteins
  - Lost dependence on normal growth promoting signals
  - Potent carcinogenic factors
  - Of the more than 200 identified, some have a risk approaching 100% to develop cancer
  - Dominant – mutation of a single allele can lead to cellular transformation
DNA damage
Oncogenic activation
Hypoxia
p53
CDK inhibitors
Cyclins D, E
CDK 2, 4, 6
Growth factors & cytokines
Proto‐oncogenes

RAS
• Most commonly mutated proto‐oncogene in human tumors
• ~30% of all human tumors contain mutated versions of RAS
• Normal RAS proteins flip back and forth between an excited signal‐transmitting state and a quiescent state.
  – Inactive – bound to GDP
  – Active – bound to GTP

• Active RAS stimulates downstream regulators of proliferation
  – Cell forced into continuously proliferating state

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Product</th>
<th>Associated Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL</td>
<td>Tyrosine Kinase (signal transduction)</td>
<td>Chronic myelogenous leukemia (CML)</td>
</tr>
<tr>
<td>C‐MYC</td>
<td>Transcription factor (nuclear regulatory protein)</td>
<td>Burkitt Lymphoma</td>
</tr>
<tr>
<td>c‐MYB</td>
<td>Tyrosine Kinase</td>
<td>Breast, Ovarian, Gastric Carcinoma</td>
</tr>
<tr>
<td>RAS</td>
<td>GTPase</td>
<td>Colon, Pancreatic Carcinoma</td>
</tr>
<tr>
<td>c‐MYC</td>
<td>Transcription factor</td>
<td>Lung Cancer</td>
</tr>
<tr>
<td>AIT</td>
<td>Tyrosine Kinase</td>
<td>Multiple Endocrine Neoplasia</td>
</tr>
<tr>
<td>C‐KIT</td>
<td>Cytokine (growth factor) Receptor</td>
<td>Gastrointestinal Stromal Tumor</td>
</tr>
</tbody>
</table>
Tumor Suppressor Genes

- Normally prevent uncontrolled growth
- Mutation (or loss) leads to transformed cell
- Usually both normal alleles must be damaged

Select Tumor Suppressor Genes

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<th>Gene</th>
<th>Gene Product</th>
<th>Associated Tumor</th>
</tr>
</thead>
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<tr>
<td>RB</td>
<td>Rb gene product blocks G1 -&gt; S phase of cell cycle</td>
<td>Retinoblastoma, osteosarcoma</td>
</tr>
<tr>
<td>p53</td>
<td>P53 gene product blocks G1 -&gt; S phase cell cycle</td>
<td>Most human cancers, Li Fraumeni syndrome</td>
</tr>
<tr>
<td>BRCA1</td>
<td>DNA repair protein</td>
<td>Breast, Ovarian Cancer</td>
</tr>
<tr>
<td>BRCA2</td>
<td>DNA repair protein</td>
<td>Breast Cancer</td>
</tr>
</tbody>
</table>
DNA damage
Oncogenic activation
Hypoxia
p53
CDK inhibitors
Cyclins D, E
CDK 2, 4, 6
Growth factors & cytokines
Proto-oncogenes
RB
• “Governor of the cell cycle”
• Retinoblastoma gene (RB)
  – 1st tumor suppressor gene discovered
  – Basis for Knudson’s two-hit hypothesis

Retinoblastoma
• Intra-ocular neoplasms of children
  – Median age at presentation 2 years
    • Poor vision, strabismus, white-ish hue to pupil
• Neuronal origin
Retinoblastoma

A. Poorly cohesive tumor in retina is seen abutting the optic nerve.
B. Higher power view showing Flexner-Wintersteiner rosettes (arrow) and numerous mitotic figures.

A. Optic nerve DNA damage
B. Oncogenic activation
C. Hypoxia
D. p53
E. CDK inhibitors

Cyclins D, E
CDK 2, 4, 6

Growth factors & cytokines
Proto-oncogenes

Growth inhibitors (e.g., p27, p5)

Growth factors (e.g., PDGF)

Phosphorylation
MAP kinase

Cyclin-dependent kinase

Hyperphosphorylation

3' UTR

13
DNA damage

Oncogenic activation

Hypoxia

p53

• "Guardian of the Genome"
• Most commonly mutated gene in cancers
• In face of stress
  – Activates temporary cell cycle arrest (quiescence)
  – Induces permanent cell cycle arrest (senescence)
  – Triggers programmed cell death (apoptosis)
Li-Fraumeni Syndrome

- Patients inherit one defective copy of p53 in the germline
- One additional “hit”
  - 25x greater risk of developing cancer by age 5
  - Sarcomas, breast cancer, leukemia, brain tumors, adrenal cortex carcinomas, multiple primary tumors

Genes that Regulate Apoptosis/DNA Repair
**Intrinsic/Mitochondrial Pathway of Apoptosis**

**Extrinsic Death-Receptor Pathway**

- Fas – Death receptor
- Caspases 8-9 initiators
- Other Caspases executioners
- Responsible for elimination of Self-reactive lymphocytes

- What happens if BCL-2 is activated by translocation?
  - Perpetuation of “anti-apoptosis”
  - Follicular B-cell lymphoma
  - t(14;18)
Total Takeover

- Loss of growth restraints is not enough
- Neoplasms Develop Limitless Replicative Potential

Telomeres

- Short, repeat sequences of DNA
- With each somatic cell duplication, small section is not duplicated... telomeres shorten
  - DNA ends appear “broken”
    - Cell cycle arrest
  - “Telomerase” – stabilizes telomere length
• Loss of growth restraints is not enough
• Limitless Replicative Potential is not enough
• Neoplasms Develop Sustained Angiogenesis

Sustained Angiogenesis

• Vascularization of neoplasms is necessary for growth
  – Nutrients, oxygen
  – New endothelial cells secrete growth factors
    • PDGF, insulin-like growth factor

• Angiogenesis
  – Inducer: VEGF
    • Hypoxia inducible factor (HIF-1α) transcription factor
    • Von-Hippel-Lindau (VHL) suppressor
  – Inhibitor: Thrombospondin 1 (TSP-1)
• Loss of growth restraints is not enough
• Development of Limitless Replicative Potential is not enough
• Sustained Angiogenesis is not enough
• Malignant neoplasms develop the ability to evade and metastasize

Sequence of events in the invasion of epithelial basement membranes by tumor cells.

- E-cadherin mediate adhesion of epithelial cells
- function lost in some cancers, facilitates detachment from primary tumor
- Degradation of basement membrane and Interstitial connective tissue
- Attachment of cells to ECM proteins
- Migration of tumor cells through degraded Basement membrane and zones of matrix proteolysis
Hallmarks of Cancer

Tumors start out as MONOCLONAL.
New subclones arise from the descendants of the original transformed cell by multiple mutations. With progression, the tumor mass becomes enriched for variants that are more adept at evading host defenses and are likely to be more aggressive.

Etiology of Cancer: Carcinogenic Agents

- Inflict Genetic Damage
  - Chemicals
  - Radiant Energy
  - Microbial Agents
Chemical Carcinogens

- Direct Acting:
  - Require no metabolic conversion
  - i.e. Cancer chemotherapeutics (alkylating agents)

- Indirect Acting:
  - Require metabolic conversion to become ultimate carcinogens
  - Polycyclic hydrocarbons
    - Benzo(a)pyrene formed in combustion of tobacco in cigarettes
  - Aromatic amines, azo dyes
    - 2-naphthylamine in dye and rubber industries
  - Susceptibility to cancer depends on allelic form of enzyme inherited

Chemical Carcinogens

- React with nucleic acids (RNA, DNA), and/or proteins
- Carcinogenicity may be augmented by agents called promoters
  - Compounds, themselves nontumorigenic, which facilitate the induction of cell proliferation (clonal proliferation)
  - “initiation-promotion” sequence
- Some chemical carcinogens may act in concert with viruses or radiation to induce neoplasias

Examples of Carcinogens

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Organ</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinyl Chloride</td>
<td>Liver</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Nitrosamine (smoked foods)</td>
<td>Stomach</td>
<td>Gastric Cancer</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Lung</td>
<td>Mesothelioma, bronchogenic carcinoma</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Skin</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Naphthalene (analine) dye</td>
<td>Bladder</td>
<td>Urothelial carcinoma</td>
</tr>
<tr>
<td>Aflatoxin B</td>
<td>Liver</td>
<td>Hepatoscellular carcinoma</td>
</tr>
</tbody>
</table>
Radiation Carcinogenesis

• Sources:
  – Sunlight - ultraviolet radiation
  – X-rays
  – Nuclear fusion/ Ionizing Radiation
  – Fission by-products
  – Radionucleotides

Radiation Carcinogenesis

Mechanism(s) of action
• Ionizing radiation:
  – Chromosome breakage, translocations, point mutations
    • Leads to genetic damage → carcinogenesis
    • Associated cancer – papillary carcinoma of thyroid
• UV light
  – Damages DNA by forming pyrimidine dimers
    • Normally repaired by nucleotide excision repair pathway
    • Associated cancers – skin squamous cell, basal cell and melanoma

Radiation Carcinogenesis

• Long latent period
• Radiation initiation is irreversible
• Continued exposure is additive
Examples

• Early radiologists - (skin cancer, leukemia)
• Fair skinned people/sun rays - (skin cancer)
• Miners of uranium - (lung cancer)
• Atomic bomb survivors - (leukemia)
• Therapeutic irradiation - (thyroid cancer)
• Patients getting multiple diagnostic radiologic scans

Xeroderma Pigmentosum
Autosomal Recessive Syndrome of Defective DNA Repair
– Defect in nucleotide excision repair pathway
– Markedly increased predisposition to skin cancers

Microbial Oncogenesis

• RNA viruses
  – Human T-cell lymphotropic virus (HTLV-1)
    • T-cell leukemia/lymphoma
• DNA viruses
  – Human papillomavirus (HPV)
    • Benign warts, cervical cancer
  – Epstein Barr Virus (EBV)
    • Burkitt lymphoma, nasopharyngeal carcinoma
  – Hepatitis B and C virus
    • Hepatocellular Carcinoma
• Bacteria
  – Helicobacter pylori
    • Gastric adenocarcinoma, MALT lymphoma
HTLV-1 infects many T cells and initially causes polyclonal proliferation by autocrine and paracrine pathways triggered by the TAX gene. Simultaneously, TAX neutralizes growth inhibitory signals by affecting TP53 and CDKN2A/p16 genes. Ultimately, a monoclonal T cell leukemia/lymphoma results when one proliferating T cell suffers additional mutations.

Spectrum of cervical intraepithelial neoplasia (CIN)

Self-check – describe/name the changes
Host Defense Against Tumors: Tumor Immunity

- “Immune Surveillance”
- What is the nature of tumor antigens?
- What host effector systems may recognize tumor cells?
- Is tumor immunity effective against spontaneous neoplasms?

### ANTITUMOR EFFECTOR MECHANISMS

- **Cytotoxic T lymphocytes**
- **Natural Killer Cells**
- **Macrophages**
- **Humoral Mechanisms**
  - No in-vivo evidence
  - However, administration of monoclonal antibodies (ie CD2) can be therapeutically effective
Host Defense Against Tumors: Tumor Immunity

- Immunosuppressed patients at increased risk for cancer development
  - Congenital immune deficiencies
  - Transplant recipients
  - AIDS
Clinical Aspects of Neoplasia

- Effects of tumor on host
  - Location
    - Compress adjacent structures
    - Ulcerate through surfaces
  - Hormone production
    - Endocrine glands

Clinical Aspects of Neoplasia

- **Cancer Cachexia**
  - Loss of body fat, lean body mass
  - Weakness, anorexia, anemia
  - Cytokine mediated
    - TNF
    - Proteolysis inducing factor
  - No satisfactory treatment if neoplasm cannot be removed

Clinical Aspects of Neoplasia

- **Paraneoplastic Syndromes**
  - Symptom complexes that cannot be readily explained by local or distant spread
  - Hormone elaboration not indigenous to tumor parenchyma
“How bad is it?”

- Grading and Staging of Cancer
  - In order to quantify the clinical aggressiveness of any given neoplasms for selection of appropriate treatment the cytological grading, and staging (size and spread of tumor) is assessed.

GRADING

- Based on cytologic differentiation of the tumor cells, an attempt is made to estimate the aggressiveness of the tumor.
  - Degree of cellular differentiation
  - Degree of cellular pleomorphism
  - Degree of loss of normal architecture
  - Mitotic index
**BENIGN THYROID TUMOR (ADENOMA)**
Well-differentiated, normal appearing thyroid follicles

**MALIGNANT COLON TUMOR (ADENOCARCINOMA)**
Well-differentiated, forming recognizable glands

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**Anaplastic Thyroid Cancer**

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**ANAPLASTIC TUMOR OF THE SKELETAL MUSCLE (RHABDOMYOSARCOMA)**
Normal Skeletal Muscle
STAGING
• Size of primary tumor
  • T1, T2, T3, or T4

STAGING
• Extent of spread to lymph nodes
  • NO, N1, I

TNM staging
• Presence or absence of metastasis
  • MO or M1
• This clinical staging system is call the "TNM" SYSTEM
• American Joint Committee (AJC) System uses 0 to IV staging system
• Staging is of greater clinical value than grading
  – Few cancers where grading has shown particular relevance
   • Prostate Cancer
   • Chondrosarcoma
DIAGNOSIS OF CANCER

• Clinical data invaluable for optimal pathologic diagnosis
  – HPI, social hx, family hx, ROS, PE
• Radiologic studies contribute significantly
• Tissue Sampling
  – Should be adequate and representative of lesion
  – Excision, biopsy, fine-needle aspiration, cytology smears

METHODS AIDING DIAGNOSIS

• Histologic and cytologic examination
• Immunohistochemistry
• Biochemistry studies
• Ultrastructural studies (electron microscopy)
• Molecular Biology Studies

Normal Cervix Cytology

Cervical Cancer Cytology
BIOCHEMICAL STUDIES: Detection of tumor associated markers

Alpha-fetoprotein (AFP):
- Liver carcinomas
- Tumor of yolk sac remnants
- Gonadal tumors

Carcinoembryonic antigen (CEA)
- Colon, Pancreas, Lung, Stomach, Breast

Markers generally more valuable for detecting recurrence of disease rather than primary diagnosis

Molecular Analysis

- Diagnosis
- Prognosis
- Detection of minimal residual disease
- Diagnosis of hereditary predisposition to cancer
- Therapeutics
Therapeutic targeting of hallmarks of cancer
FIN

Questions ???
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