Cancer Pathophysiology

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Learning Objectives:
1. Describe the pathophysiology of cancer cells
2. Distinguish between benign and malignant pathological findings
3. Analyze Pathology Findings

Agenda
• Pathophysiology of Cancer Cells
  – Regulation of cell growth
  – Molecular biology of cancer
  – Cancer histology
  – Grading systems/novel biomarkers
  – Focus or breast cancer biology
• Interactive case studies on:
  – Breast, colon, lung cancers

Some questions we will consider:
• How is cell growth regulated?
• What is cancer?
• What causes cancer?
• How do cells progress from normal – cancerous?
• How is cancer diagnosed?
• Which cancers are generally treatable?

Some Terms:
• NEOPLASIA
  – New growth, abnormal cells
  – Growth can be benign or malignant
    • Eg: Benign – wart; Malignant – cancer
• Benign neoplastic cells
  – Grow at the wrong rate or wrong place
  – Usually do not require intervention
  – Do not metastasize
• Malignant neoplastic cells
  – No useful function
  – Harmful to body tissues, always abnormal, metastasize
Learning Activity
Identify the origin of these cancers:
• Carcinoma
• Adenocarcinoma
• Sarcoma
• Lymphoma
• Glioma
• Leukemia

Basic Cancer Biology

• Question 1:
  – A cancer derived from connective tissue is a:
    a) carcinoma
    b) myeloma
    c) sarcoma
    d) glioma

How is Cell Proliferation Regulated?

Cell Growth and Differentiation

• Cells are stimulated to progress through the cell cycle and to differentiate by various growth factors.
• Cellular growth is regulated by a system of “Stop” and “Go” signals, as depicted in the following slide:

How is cells growth initiated?
How is cell growth regulated?

Learning Activity:
What are characteristics of cancer cells?

BIOLOGY OF ABNORMAL CELLS

• Benign tumor cells:
  – Examples: moles, nerve ganglia, cysts, uterine fibroid tumors, endometriosis
  – Characteristics of Benign cells:
    • Inappropriate cells growth
    – Benign tissues unnecessary for normal functions
    – Examples: moles, nerve ganglia, cysts, uterine fibroids, endometriosis, rectal polyps
    • Strongly resemble parent cells; retain morphology of tissue of origin
    • Specific differentiated functions
    • Joined tightly together
    • Do not migrate
    • Small nucleus to cytoplasm

• Cancer Link: Receptor, transducer, transcription factor may become constitutively activated

• Cancer Link: Receptor, transducer, transcription factor may become ‘knocked-out’ or mutated

BIOLOGY OF ABNORMAL CELLS

Malignant Tumour cells:
  – Appearance changed from cells of origin
  – Size and shape make identification of the origin more difficult
  – Poorly controlled growth continuous cell division and growth
  – Growth compared to the parent cell
    – E.g. bone marrow cells divide rapidly, leukemia cells divide rapidly
  – Large nucleus to cytoplasm ratio
  – Loss of differentiated functions/appearance
  – Migrate through blood vessels and tissues
  – Altered surface proteins
    – break away from tumor with only slight pressure
    – No contact inhibition
    – continue to divide even when they come in contact with other cells

Learning Activity

• Differentiate between the following:
  – Hyperplasia
  – Dysplasia
  – Metaplasia
• How do they relate to cancer risk?

Basic Cancer Biology

• Question 2:
  – Which one of the following cellular adaptations is both predictive of cancer and reversible?
    a) Metaplasia
    b) Atrophy
    c) Hyperplasia
    d) Dysplasia
Basic Cancer Biology Questions

• Question 2 Answer:
  – Which one of the following cellular adaptations is both predictive of cancer and reversible?
  a) Metaplasia
  b) Atrophy
  c) Hyperplasia
  d) Dysplasia

Molecular Biology of Cancer

A disease of abnormal growth, division, and cell differentiation

TRANSFORMATION: FOUR STEPS

INITIATION

PROMOTION

PROGRESSION

METASTASIS

Initiation

• Normal cell’s proto-oncogenes are activated
  – Proto-onco-genes regulate early rapid cellular growth of embryonic life and become repressed after birth
• An event or exposure that can damage DNA may damage the genes of a normal cell turning on genes that should remain repressed
• Carcinogens alter gene activity such that the cell acquires malignant characteristics
  – May be viral, chemical, physical agents

Promotion

• After a cell becomes initiated, it usually takes some time before a cell becomes cancer
• Latency period is the time from when a cancer is initiated until it becomes a cancer cell
• Promoters are substances that shorten the latency period by promoting or enhancing cell growth
  – Eg: hormones, drugs, and many industrial chemicals.

Progression

• Eventually cancer cells grows enough to form a detectable tumor
• 1cm tumor = approx. 1 billion cells
• To grow further, a tumor must have a blood supply
  – Until the tumor reaches 1 cm it gets fluids by diffusion from surrounding cells
  – After 1 cm it must get it’s own blood supply
  – Angiogenesis factors cause capillaries and other blood vessels to grow new branches into the tumor
• Original tumor arising from the transformed tumor cells is called the primary tumor
**Metastasis**

- Occurs when cancer cells move from the primary site to more remote sites
- Called metastatic or secondary tumors
  - Examples of primary, secondary tumors:
    - Lung to the brain
    - Breast to bone, brain, liver

**Proto-oncogenes**

- Genes that confer an advantage to tumor though gain-of-function mutation
  - Activated counterparts are oncogenes
  - Examples:
    - HER2/neu
      - growth factor receptor; breast cancer
    - B-raf
      - signal transduction; melanoma
    - Myb
      - transcription factor; leukemia

**Tumor Suppressor Genes**

- Genes that confer an advantage to tumor though loss-of-function mutation
  - More common than oncogenes
  - Examples:
    - Rb (cell cycle regulator; neuroblastoma)
    - APC (cell adhesion; colon cancer)
    - BRCA1&2 (DNA repair; breast cancer)

**Basic Cancer Biology**

- Question 3:
  - An proto-oncogene is best defined as:
    a) a gene that transforms normal cells into tumor cells
    b) a gene which, when mutated can cause cancer
    c) a tumour-suppressor gene
    d) a gene that causes dysplasia

**Basic Cancer Biology**

- Question 3 Answer:
  - An proto-oncogene is best defined as:
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    d) a gene that causes dysplasia

**Why do cells cancer cells become ‘immortal’?**

The role of Telomerase
Telomerase and Ovarian Cancer

• In certain types of ovarian cancer, an enzyme known as TELOMERASE is over-expressed
• Telomerase enzyme
  – replaces telomeres on the ends of chromosomes
  – Normally expressed at low levels
  – Over-expressed in some cancers

Telomeres

• The center of a chromosome is called the CENTROMERE
• At either end of a chromosome are multiple TELOMERES
• These are nucleoprotein repeats which contain no coding information

Worn-Out Chromosomes

• Normally, during cell division, telomeres are lost
  – Due to mechanical wear?
• After enough cell divisions, coding regions of the chromosome are also lost
• This is likely one reason why non-cancerous cells can only divide a finite number of times

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• Question 4: Which one of the following statement is correct with respect to telomeres?
  a) They increase in number with age
  b) They increase in number certain type of ovarian cancers
  c) They are inhibited by the enzyme telomerase
  d) They are antiinflamatory

Basic Cancer Biology

• Question 4 Answer:
  – Which one of the following statement is correct with respect to telomeres?
    a) They increase in number with age
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    d) They are antiinflamatory

Histopathology of Tumors

Benign and Malignant Tumors
Benign Epithelial Tumors

- Adenomatous Polyp (colon)
  - Note:
    - abnormal epithelium (villi are different)
    - Cellular dysplasia

- Fibroadenoma of the breast
  - Nodule is solitary, encapsulated, firm and mobile
  - Note lobulated appearance

- Squamous cell papilloma
  - The tumors look like normal keratinocytes; they are increased in number
  - Acanthosis
  - Hyperkeratosis

- Fibroadenoma of the breast
  - A. Stromal proliferation compresses ducts
  - Intracanalicular fibroadenoma
  - B. Fibrous stroma proliferates around ducts
    - Pericanalicular fibroadenoma

Malignant Epithelial Tumors

- Adenocarcinoma
  - From colorectal mucosa
  - Note irregular glands

- Invasive Ductal Carcinoma
  - Note:
    - atypical tumor cells form ribbons or nests
    - Basement membrane is disrupted
Malignant Connective Tissue Tumors

- **Fibrosarcoma**
- **Note:**
  - 'Fishbone' appearance
  - Lots of mitotic figures
- **Also present:**
  - Immature blood vessels

Lymphomas

- **Hodgkin’s**
- **Note:**
  - Reed-Sternberg Cell
  - Mirror-image nuclei ('owl eyes')

- **Non-Hodgkin’s**
- **malignant melanoma**
- **Note:**
  - Regular lymph node architecture is gone
  - Tumor lymphocytes look normal but are functionally immature

Basic Cancer Biology

- **Question 5:**
  - A pediatric tumor found primarily in children, which originates in the kidney and causes hematuria and pyrexia is:
    a) Wilm’s tumors
    b) Barret’s tumor
    c) Pheochromocytoma
    d) Ewing sarcoma

- **Question 5:**
  - A pediatric tumor found primarily in children, which originates in the kidney and causes hematuria and pyrexia is:
    a) Wilm’s tumors
    b) Barret’s tumor
    c) Pheochromocytoma
    d) Ewing sarcoma
Cancer Detection

Finding a Mass
• Usually begins with the detection of a mass or a lesion
  – Physical detection, medical imaging
  – Recall that a mass of 1cm has approximately 1 billion cells
• We also have a variety of biological markers
  – Can you list a few of the common markers?
    • ... there is a sampling on the next few slides

Detecting a Cancer Antigen
• Carcinoembryonic antigen
  – Many solid tumours
• Alpha fetoprotein
  – Liver, ovary, testicular tumours
• CA 19-9, CA 27-29, CA 15-3
  – For staging breast cancers
• Prostate-specific antigen
  – Prostate CA
• Human Chorionic Gonadotropin
  – Ovary

Detecting other Cancer Markers
(Ectopic Hormones)
• Human Chorionic Gonadotropin (HCG)
  – Many tumours
• ACTH, ADH, MSH
  – Lung tumours
• TSH
  – Placental tumours (choriocarcinoma)
• Insulin
  – Lung

Basic Cancer Biology
• Question 6:
  – Which statement regarding the use of tumor markers is correct?
    a) Tumor markers are only produced by malignant conditions
    b) Prostate specific antigen testing is more efficacious when combined with digital rectal exams
    c) The Ca125 marker is specific for breast cancer
    d) Alpha-fetoprotein is most predictive for lung cancer

Basic Cancer Biology
• Question 6 Answer:
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    c) The Ca125 marker is specific for breast cancer
    d) Alpha-fetoprotein is most predictive for lung cancer
Basic Cancer Biology

• Question 7:
  – An ectopic hormone which may be a marker for lung cancer includes:
    a) Thyroid hormone
    b) Human chorionic gonadotropin
    c) Estrogen
    d) Insulin

Basic Cancer Biology

• Question 7 Answer:
  – An ectopic hormone which may be a marker for lung cancer includes:
    a) Thyroid hormone
    b) Human chorionic gonadotropin
    c) Estrogen
    d) Insulin

Cancer Isoenzymes

• Acid Phosphatase
  – Breast, prostate CA (relatively non-specific)
• Alkaline Phosphatase
  – Placental Alk. Phos. – chorioncarcinoma, ovary, breast pancreas
  – Nonplacental Alk. Phos. – osteogenic sarcoma, parathyroid
• Galactosyl transferase
  – Lung, breast, esophagus, stomach Ca’s
• Aminopeptidases
  – Pancreas
• Gamma-glutamyl transpeptidase
  – Pancreas, stomach lining, liver
• Ribonuclease
  – Pancreas
• Sialyltransferase
  – Pancreas

CLASSIFICATION OF CANCER

• A means of standardization of diagnosis, prognosis, and treatment
• Based on cellular characteristics and activity
• Allows predictions about aggressiveness of the tumor, how it may respond to treatment
• Grade Levels 1 through 4 (higher grade = more aggressive tumor)
  – Grade 1: Low grade
    • cells similar to parent cells
  – Grade 2: low to moderate malignancy
    • cells have some normal some malignant features
  – Grade 3: Moderate to high grade malignancy
    • cells have more malignant features
  – Grade 4: High-grade malignancy
    • cells have no normal cell appearance

STAGING OF CANCER

• Allows the pinpointing of the exact location and degree of cancer spread (metastasis) of a tumor. Tumor stage influences treatment
  – Smaller tumor, less spread, better prognosis
• Three types of staging:
  – Clinical
    • tumor size, degree of mets, lymph nodes, enlarged organs
    • Based on clinical tests, CT scans, biopsy.
  – Surgical staging
    • inspection at surgery, tumor size, sites, degree of mets.
  – Pathological staging
    • most definitive, tumor size, number, sites, degree of mets, determined by pathologic exam at surgery
• Site-specific staging
  – Dukes D Colon cancer, invasion of the wall of the bowel, Clarke’s Levels of skin cancer

T.N.M. Staging:

• Done universally, allows a common language for patients with cancer. The language of this staging allows a patient to be seen at another place for second opinions or therapy.
  – T= Tumor size,
  – N= lymph node involvement.
  – M= Metastasis
• Letters after headings indicate extent of disease
Primary Tumor

- TX: cannot be evaluated
- T0: No evidence of primary tumor
- Tis:
  - Carcinoma in situ (CIS); abnormal cells are present but have not spread to neighboring tissue
  - although not cancer, CIS may become cancer and is sometimes called preinvasive cancer
- T1, T2, T3, T4: Size and/or extent of the primary tumor

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be evaluated
- N0: No regional lymph node involvement
- N1, N2, N3: Degree of regional lymph node involvement (# and location of lymph nodes)

Distant Metastases (M)

- MX: Distant metastasis cannot be evaluated
- M0: No distant metastasis
- M1: Distant metastasis is present

Learning Activity

- A 44 year old female client has a breast biopsy. The pathology report states: T3 N2 M0

  - What does this tell you?

TMN and Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Stages I, II, and III</td>
<td>Higher numbers indicate more extensive disease: larger tumor size and/or spread of the cancer beyond the organ in which it first developed to nearby lymph nodes and/or tissues or organs adjacent to the location of the primary tumor</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Cancer has spread to distant tissues or organs</td>
</tr>
</tbody>
</table>

Learning Activity

- A 74 year old male client with bladder cancer has a pathology report that states T3 N0 M0

  - What stage is this?

- An 80 year old female client has colon cancer that states T3 N0 M0

  - What stage is this?
### Other Classification Systems
- **Brain and Spinal cord**
  - Staged according to cell type and grade
- **Lymphomas**
  - Ann Arbor staging classification
- **Gynecological cancers**
  - FIGO classification based on TMN

### Tumor Grading
- **Histological approach**
  - ‘well differentiated’ (G1):
    - Cells and tissue close to that of the host
  - ‘undifferentiated’ (G4):
    - Cells and tissues completely lack normal structure
- **GX:** grade cannot be assessed
- **G2 and G3** are intermediate grades

### What’s in a Pathology Report?
- **Diagnosis**
- **Histology**
- **Tumor Size**
  - Most often metric
- **Tumor Stage**
- **Tumor Grade**
  - For Breast Ca, most common is Nottingham
- **Cytogenetics and special tests**

### Other Descriptors
- **Nuclear grade**
  - How much do nuclei look like normal nuclei?
    - Higher the grade, more abnormal the nuclei
- **Hormone Receptor Status**
  - Estrogen/Progesterone
    - For Breast Ca
  - *Her2/neu status*

### More on HER2/neu
- **Human Epidermal Growth factor receptor 2**
- **How is this determined?**
  - Immunohistochemistry
    - Amount of protein on surface
      - Done first; if score is +2 or borderline, then we do...
    - FISH (Fluorescence in situ Hybridization)
      - Tells you number of genes

### Other Data in a Pathology Report
- **Tumor Margins**
  - Positive, close, negative
- **Vascular Invasion**
  - May suggest a more aggressive tumor
- **Lymph Node Status**
  - Accuracy still unclear
Basic Cancer Biology

• Question 8:
  – HER2/Neu is:
  a) an apoptosis receptor
  b) a factor which immortalizes cells
  c) a marker for pancreatic cancer
  d) a growth factor receptor

Basic Cancer Biology

• Question 8 Answer:
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Novel Cancer Biomarkers

DNA Methylation Markers
microRNAs
SNPs

DNA Methylation Markers

– Addition of a methyl group
  – occurs in the dinucleotide 5’-CpG-3’

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So What?

• MANY cancers have ‘hypermethylated’ gene promoters

<table>
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<tr>
<th>Cancer</th>
<th>Hypermethylated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>p16INK4b, p14ARF, MGMT (DNA repair), p16, p15, p19, APC, PTEN, MYC, NOTCH1</td>
</tr>
<tr>
<td>Breast</td>
<td>TGFβ, E-cadherin, β-catenin, CYP1B1, AR, PR, TNFR1, MAPK, PI3K, PTEN, RAS, MYC</td>
</tr>
<tr>
<td>Lung</td>
<td>p16INK4b, AR, BRCA1, MGMT (DNA repair), p16INK4b, TGFβ, E-cadherin, CYP1B1, PTEN</td>
</tr>
<tr>
<td>Leukemia</td>
<td>TGFβ, E-cadherin, β-catenin, CYP1B1, AR, PR, TNFR1, MAPK, PI3K, PTEN, RAS, MYC</td>
</tr>
<tr>
<td>Bladder</td>
<td>p16INK4b, TGFβ, E-cadherin, β-catenin, CYP1B1, AR, PR, TNFR1, MAPK, PI3K, PTEN</td>
</tr>
<tr>
<td>Kidney</td>
<td>TGFβ, E-cadherin, β-catenin, CYP1B1, AR, PR, TNFR1, MAPK, PI3K, PTEN, RAS, MYC</td>
</tr>
<tr>
<td>Prostate</td>
<td>TGFβ, E-cadherin, β-catenin, CYP1B1, AR, PR, TNFR1, MAPK, PI3K, PTEN, RAS, MYC</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>TGFβ, E-cadherin, β-catenin, CYP1B1, AR, PR, TNFR1, MAPK, PI3K, PTEN, RAS, MYC</td>
</tr>
<tr>
<td>Stomach</td>
<td>p16INK4b, p14ARF, p15INK4b, p150, p19, MGMT (DNA repair)</td>
</tr>
<tr>
<td>Liver</td>
<td>TGFβ, E-cadherin, β-catenin, CYP1B1, AR, PR, TNFR1, MAPK, PI3K, PTEN, RAS, MYC</td>
</tr>
<tr>
<td>Others (Leukemia)</td>
<td>TGFβ (immunosuppression), p16INK4b, p150, p19, MGMT (DNA repair), p16INK4b, TGFβ</td>
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(Adapted from Qureshi et al, 2010)

microRNAs

• These are NON-CODING RNA molecules
  – Silence RNA, regulate gene expression
  – Present in plasma, serum, urine, saliva

• Breast, lung, colorectal cancers all have specific microRNAs which are either increase or decrease
microRNAs

SNPs

• ‘Single Nucleotide Polymorphisms’
  – A DNA sequence variation in which ONE nucleotide is different from the rest of the population

So What?

• The presence of SNPs in many genes are associated with increased risk of breast, colon, prostate and numerous other Ca’s
  – Possible role as biomarkers and in diagnostics are being evaluated

Traditional Chemotherapies

• Some Solutions
  – Most cancer chemotherapies are designed to “hit” cell replication
  – A problem:
    – This approach is non-specific
    – Most cancer chemotherapies kill cancer cells only slightly faster than normal cells

Targets of Anticancer Drugs:

Cell Cycle-Dependent vs. Cell-Cycle Independent Drugs

• Some drugs kill cancer cells only at certain phases of the cell cycle:
  – Eg: Cytochalsin
  – Works only when a high proportion of cells are dividing
• Some drugs work throughout cell cycle:
  – Eg: Cisplatin

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Newer Chemotherapies

- These are based on a more intimate knowledge of cancer biology

Goals of Cancer Treatments

- Curative
  - Total eradication of cancer cells possible?
  - The concept of “log kill”
    - If 10^9 cells present, and tmt kills 99.999%, then 0.001% left
    - This is a 5-log kill
- Palliative
  - Alleviation of symptoms
  - Avoidance of life-threatening toxicity

Learning Activity

- Which cancers respond well to pharmacotherapy?
- Which cancers do not respond well?

Etiology of Breast Cancer

- Approx. 30% of cases due to endogenous factors (genetics)
- Approx. 90% develop in ductal epithelial cells
- Newer biopsy methods include Nipple Aspiration, which can be more helpful than more common biopsy methods, since you can directly sample ductal cells
- There are several well-characterized cancer susceptibility genes
  - what are they?
- Environmental factors also certainly play major roles
- Molecular mechanisms are not well understood
Breast Cancer Facts

- Most common neoplastic disease in women
  - 1 in 9 women will receive a Dx of breast cancer by age 85
  - 30% of women diagnosed and treated for breast cancer will develop secondary mets
- Known risk factors account for only 40-50% of breast cancer cases

Breast Cancer Risk Factors

- BRCA1 and BRCA2 susceptibility genes
- Familial Hx of:
  - Breast, ovarian, endometrial Ca
- Individual Hx of:
  - Breast diseases
  - Alcohol consumption
  - Exposure to ionizing radiation
  - Endocrine/reproductive factors

Basic Cancer Biology

- Question 9:
  - Which one of the following statements regarding breast cancer is INCORRECT?
  a) Approximately 90 percent of breast cancers begin in ductal epithelial cells
  b) Polymorphisms in Phase I enzymes may account for differences in the occurrence despite similar exposure
  c) Inflammatory breast cancer usually presents as a ‘peau d’orange’ swelling
  d) The cure rate for DCIS is up to 90%

Basic Cancer Biology

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Hormonal Theory of Breast Cancer

- Reproductive risk factors include:
  - Early puberty, late menarche, short duration of breast feeding, nulliparity, delayed child birth
- Theory:
  - Prolonged exposure to estrogen may initiate breast cancer

Effects of Estrogen on Cells

- Estrogen/Estrogen-like Molecules Induce Cell-Proliferation Genes
- Estrogen/Estrogen-Like Metabolites Form DNA Mutations

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Estrogen from Two Sources May Initiate Breast Cancer:

- **Exogenous Estrogen**
  - Androsterone
  - Testosterone
  - Estrone
  - Estradiol

- **Endogenous Estrogen**
  - Due to aromatase Overexpression

Exposure to Estrogen-like Compounds Confers Risk of Breast Cancer

They may bind to same receptors, yield similar metabolites

---

Estrogens and estrogen-like compounds are metabolized to highly electrophilic molecules that bind DNA

- **Phase I Enzymes**
  - CYP17
  - Benzo[a]pyrene

DNA Adducts

Why are they problematic?

- Adducts may disrupt key regulatory pathways in ductal cells
  - Eg: p53, ras
- Adducts can cause gene mutations:

Sources of Pseudo-estrogens and PAHs

- **Pseudoestrogens**
  - Plastics
- **Phytoestrogens**
  - Soy, isoflavones
- **PAHs**
  - Engine exhaust
  - Over-cooked meat
  - Coal tar

So, given similar exposures, why do some women get breast cancer while others do not?
Polymorphisms in estrogen-metabolism genes:

Blocking Estrogen Receptors

- Principle drug has been TAMOXIFEN
  - Competes with estradiol for binding sites
  - Works in some ER+ cancers
  - Often used in breast cancers which have metastasized to bone
    - May cause pain in affected site: a GOOD sign!
    - May cause eye damage

Basic Cancer Biology

- Question 10:
  - Increased lifetime exposure to estrogen is considered a risk factor for certain cancers due to:
    a) metabolism of estrogen to form DNA adducts
    b) the suppressive effect of estrogen on cell growth
    c) suppression of the immune system
    d) Estrogen inhibiting aromatase

Basic Cancer Biology

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Aromatase Inhibitors

A Newer Class of Breast Cancer Drugs
NOT ER+ Dependant

Estrogen from Two Sources May Initiate Breast Cancer:

- Exogenous Estrogen
- Endogenous Estrogen Due to aromatase overexpression
Aromatase Inhibitors

• While Tamoxifen blocks a tumor’s ability to use estrogen, AI’s reduce the amount of estrogen in the body
• Examples of AI’s currently approved:
  – Anastrozole (Arimidex®)
  – Exestane (Aromasin®)
  – Letrozole (Femara®)

Her2 Therapies

• In about 20% of breast Ca, cells overexpress HER2/neu
• Some novel immunotherapies:
  – Trastuzumab (Herceptin)
  – Pertuzumab (Perjeta)
  – Ado-trastuzumab emtansine (Kadcyla)
  – Lapatinib (Tykerb)

  – What are the targets of Herceptin and Perjeta?

Triple Negative Breast Cancer

• Absence of:
  – Estrogen receptor
  – Progesterone receptor
  – HER2/neu
• Approx. 20% of all breast Ca
• Emerging therapy:
  – PARP inhibitors

A Word on Breast Tumours

• Stage and location of a tumour is important with respect to both treatment and prognosis
• It is not the primary tumour which causes morbidity and mortality, it is the metastases
• This makes diagnosis and treatment even more complicated, since the mets can be quite different from the primary tumour

The Conundrum

• Before a tumor is detected by physical exam, nearly half a billion cells must be present
• Many molecular markers for breast cancer are only for the primary site

So, where do we go from here?

• Establish biomarkers of exposure and response
  – Determine exposure level AND response to environmental contaminants
    – Eg: aside from BRCA1 and 2, does a woman have specific isoforms of Phase I and II enzymes which place her at increased risk?
• Other avenues:
  – Prophylactic treatment
    – Example: Cytochrome Therapies
  – Environmental assessment
    – Determining the risk of exposure to environmental factors
  – Life-style changes
    – If you DO have certain markers, perhaps diet/other factors can be modified to reduce risk of exposure
  – Altering the environment
Interactive Case Studies

• Colon Cancer

• Breast Cancer

Case Study 1

• OM is a 51 yo old African American male
  – experiencing severe RLQ abdominal pain (9/10)
  – Abdominal CT revealed a 5-cm tumor
    • surgically resected, no visible signs of disease
    • no sign of liver or lung involvement on CT scan
  – Pathology:
    • Poorly differentiated adenocarcinoma
    • Transmural penetration deep and perforation of visceral peritoneal
    • Consistent with stage IIB

Case 1

• Question 1:
  – What is the current 5-year survival rate for non-metastatic Stage IIB colon cancer?
  a) 30%
  b) 50%
  c) 70%
  d) 90%

Case 1

• Question 1 Answer:
  – What is the current 5-year survival rate for non-metastatic Stage IIB colon cancer?
  a) 30%
  b) 50%
  c) 70%
  d) 90%

Case Study 1 Continued

• OM
  – At time of surgery:
    • Serum CEA was 15.7 ng/mL
  – Post-Surgery
    • Patient underwent six cycles of combination chemotherapy over 5 weeks
    • Post chemo
      • chest and abdominal CT scans negative; serum CEA 3.2 ng/mL.
  – However, one year later:
    • OM noticed bright red blood in stool
    • O/E:
      • Fluid wave consistent with ascites noted
      • Serum CEA now 23.4 ng/mL
      • Exploratory laparotomy:
        • recurrent cancer in the terminal ileum, descending colon
        • CT and U/S were performed to look for possible mets

Case 1

• Question 2:
  – What is the current 5-year survival rate for metastatic colon cancer?
  a) 50%
  b) 30%
  c) 10%
  d) 5%
Case 1

• Question 2 Answer:
  – What is the current 5-year survival rate for metastatic colon cancer?
  a) 50%
  b) 30%
  c) 10%
  d) 5%

Case Study 1

• Question 3:
  – From the lab panel, which organ is likely involved with mets?
  a) Pancreas
  b) Liver
  c) Spleen
  d) Kidney

<table>
<thead>
<tr>
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<tr>
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• Question 3 Answer:
  – From the lab panel, which organ is likely involved with mets?
  a) Pancreas
  b) Liver
  c) Spleen
  d) Kidney

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Case Study 1

• Question 4:
  – Again from the lab panel, which would of the following indices is consistent with ascites?
  a) Bilirubin
  b) LDH
  c) Albumen
  d) BUN

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Case Study 1 Continued

• Current Labs:

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Case Study 1

• Question 4 Answer:
  – Again from the lab panel, which would of the following indices is consistent with ascites?
  a) Bilirubin
  b) LDH
  c) Albumen
  d) BUN
Case Study 2:

- LM is a 50-year-old female presenting with R. breast microcalcifications on mammography.
- O/E:
  - No palpable breast masses, no nipple discharge, no abnormal retraction.
- PMH:
  - Diverticulosis and tubular adenoma
- PSH:
  - Colonoscopy
- Risk factor assessment:
- FH:
  - Mother diagnosed with breast cancer age 59, sister diagnosed age 45, maternal grandmother some type of cancer (?), father with colon cancer.
- PE:
  - Breast right with core biopsy healing site at 9 o’clock, no masses, no nipple discharge, no abnormal retraction, no axillary or supraclavicular adenopathy.

Case Study 2: Mammogram Results

Left Breast
Right Breast

Case Study 2: Histological Findings

- Microcalcifications
- Necrotic cells
- Mitotic Figures
- Ductal Cell Hyperplasia
- High Nucleus: Cytoplasm Ratio

Case Study 2

- Question 1:
  - What percentage of non-palpable breast cancers are detected by mammography as microcalcifications?
  a) 10%
  b) 30%
  c) 50%
  d) 70%

Case Study 2

- Question 1 Answer:
  - What percentage of non-palpable breast cancers are detected by mammography as microcalcifications?
  a) 10%
  b) 30%
  c) 50%
  d) 70%

Case Study 2

- Question 2:
  - All DCIS is considered stage 0 breast cancer
  a) True
  b) False
Case Study 2

• Question 2 Answer:
  – All DCIS is considered stage 0 breast cancer
    a) True
    b) False

• Question 3:
  – Higher grade DCIS have fewer mitotic figures
    a) True
    b) False

Case Study 2

• Question 3 Answer:
  – Higher grade DCIS have fewer mitotic figures
    a) True
    b) False

Final Words

• Clearly, there is much more that could have/should have been covered
• What I have attempted to do is summarize some of this information for you and to put an individual ‘spin’ on it
• If you have any expertise you would like to share, please feel free to do so …