

**Neoplasia I**  
**Definitions, Terminology, and Morphology**  
  
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Tissue Type	Cell Type	Benign	Malignant
Conn. Tissue	Fibroblast	Fibroma	Fibrosarcoma
	Adipocyte	Lipoma	Liposarcoma
	Cartilage	Chondroma	Chondrosarcoma
	Bone	Osteoma	Osteosarcoma
Vessels, etc	Endothelial cells	Hemangioma	Angiosarcoma
	Meninges	Meningioma	Invasive meningioma
Muscle	Smooth muscle	Leiomyoma	Leiomyosarcoma
	Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Epithelium	Stratified Squamous	Squamous papilloma	Squamous cell carcinoma
	Ducts or glands	Adenoma	Adenocarcinoma
Melanocytes	Melanocytes	Nevus	Melanoma

Cancer - second leading cause of deaths in the US after CV disease

- Characteristics of Benign & Malignant Neoplasms**
- Tissue Architecture – histologic features
  - Cytologic features
  - Terminology
    - Differentiation/anaplasia
    - Dysplasia
    - Rate of growth
    - Local Invasion
    - Metastasis

- Nomenclature**
- Neoplasia “new growth”
  - Neoplasms arise from genetic changes that allow excessive, unregulated cell proliferation
  - Cell type of parenchyma + OMA

- Characteristics of Benign & Malignant Neoplasms**
- **Tissue architecture**
    - **Benign** - well circumscribed, usually encapsulated
    - **Malignant** – poorly circumscribed, lack of cell polarity and epithelial cell connections

### Characteristics, con't.

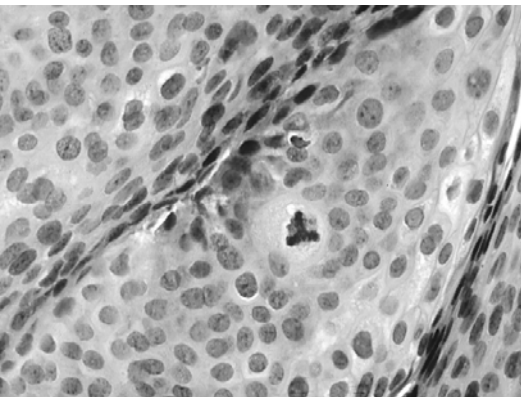
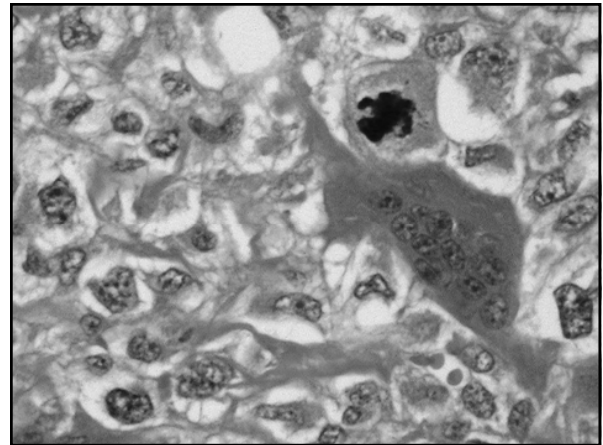
- **Cytologic features**
  - **Benign** – small, uniform cells, no visible nucleoli
  - **Malignant** – large, pleomorphic cells with large hyperchromatic nuclei, N:C ratio 1:1 (nl. 1:4), large nucleoli, irregular nuclear outlines

### Anaplasia

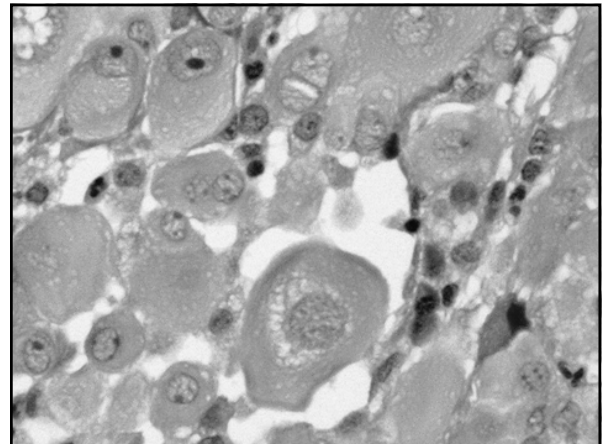
- Neoplasm without apparent differentiation, undifferentiated cells

### Differentiation

- Refers to original parenchymal cell, tissue appearance and function
  - **Benign** - well differentiated, resembles cell of origin with few mitoses, secretion of products, hormones, mucins, etc.
  - **Malignant** - well to poorly differentiated with numerous, bizarre mitoses



Abnormal mitosis

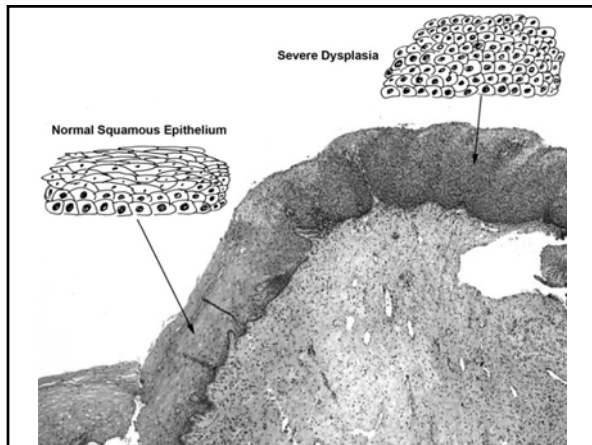


### Dysplasia

- Disorderly cellular maturation
- If, full epithelial involvement –carcinoma in situ, pre-invasive stage
- HPV – cervix
- Smoking- respiratory tract
- GERD – esophagus

### Local Invasion

- Benign – most encapsulated and cannot invade or spread to other sites
- Malignant – not encapsulated and can invade

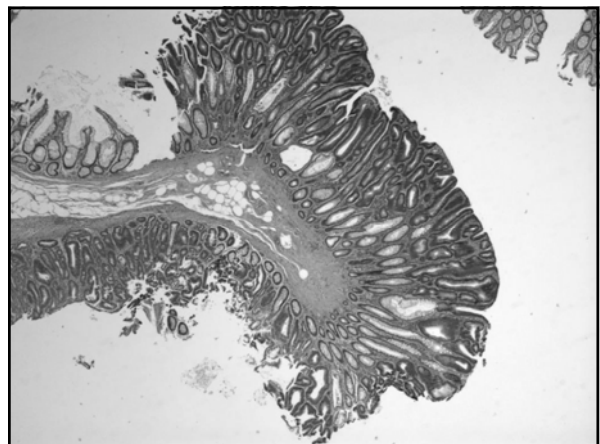


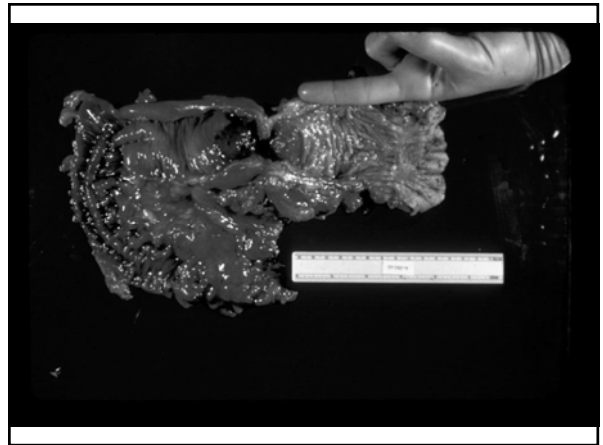
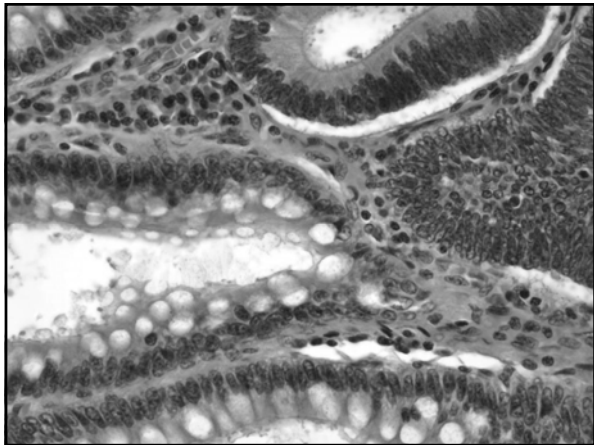
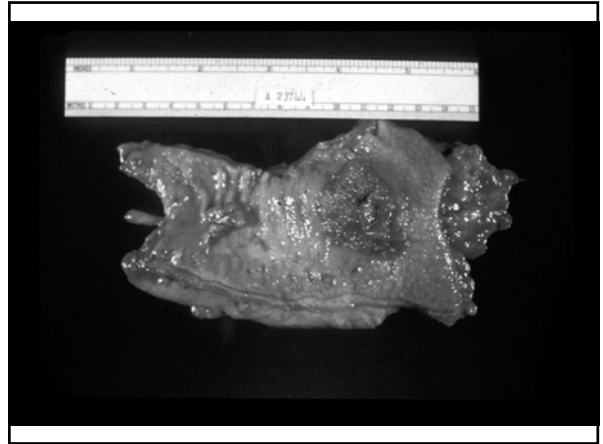
### Benign Neoplasia

- Remains localized
- Cannot spread to other sites
- Most patients survive, but some tumor locations can cause serious problems (brain stem, spinal cord, pituitary)

### Rate of Growth

- Benign – slower growth, some dependent on hormones, leiomyoma
- Malignant – more rapid growth, areas of necrosis

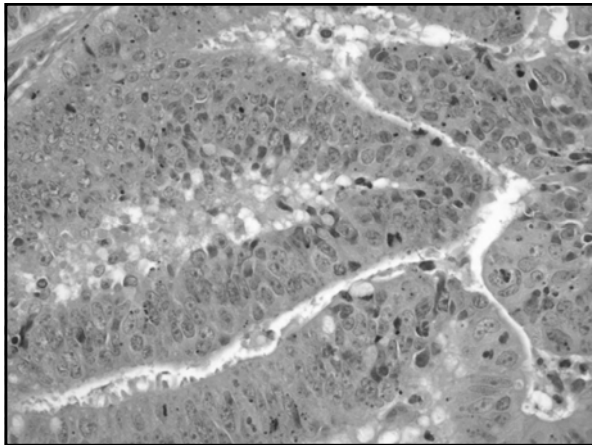
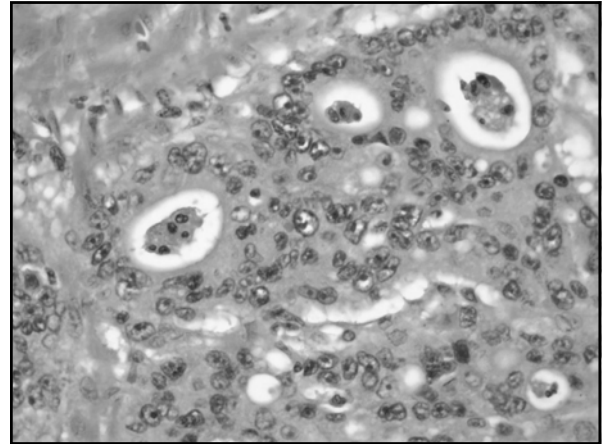
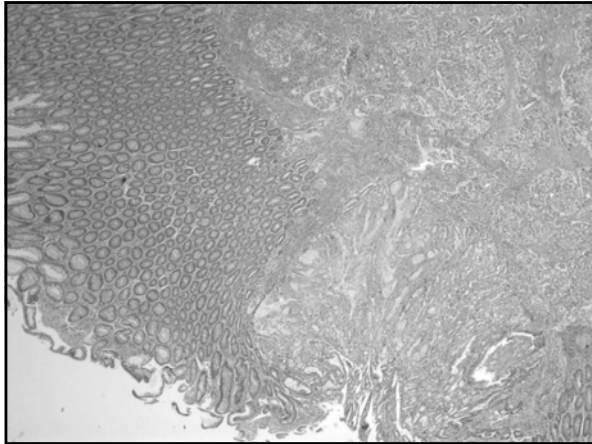




**Malignant Neoplasia**

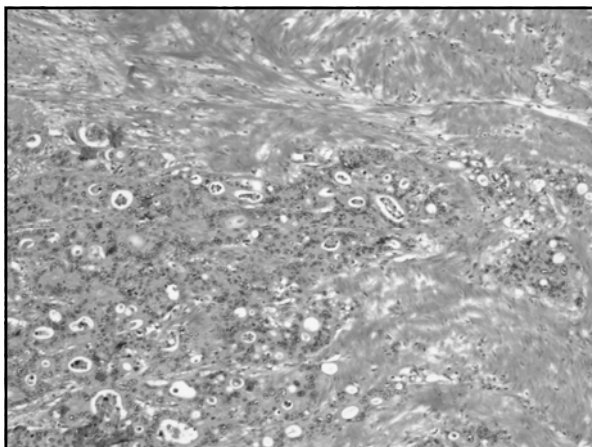
- Can invade and destroy adjacent tissue
- Can spread to distant sites, metastasis





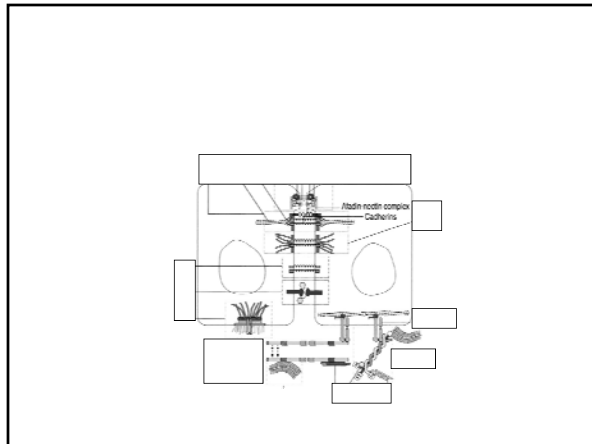
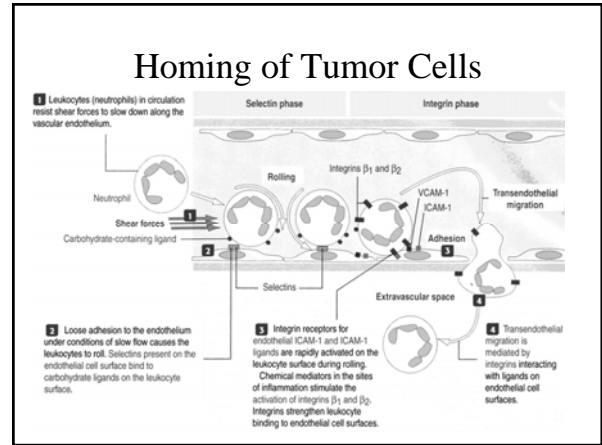
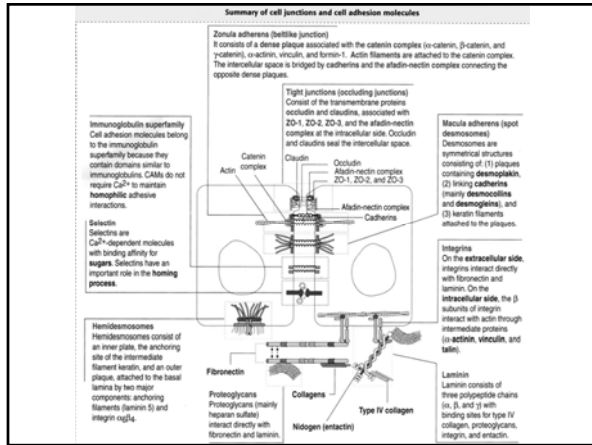
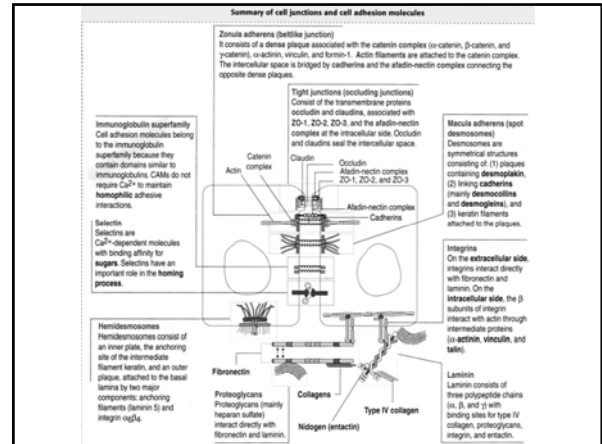
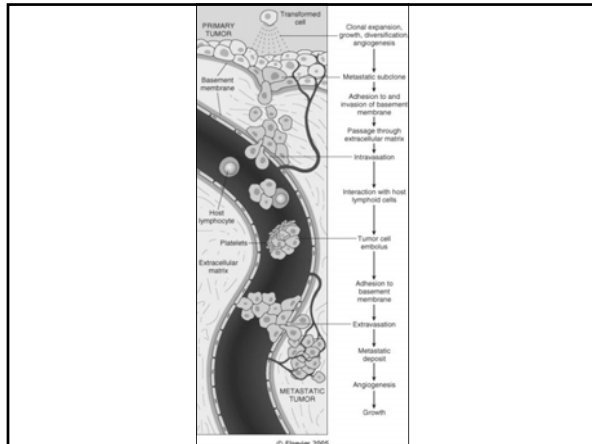
**Metastasis**

- Dissemination to other organs:
  - Seeding of body cavities (ovary)
  - Lymphatic spread (carcinoma)
  - Hematogenous dissemination (sarcoma)

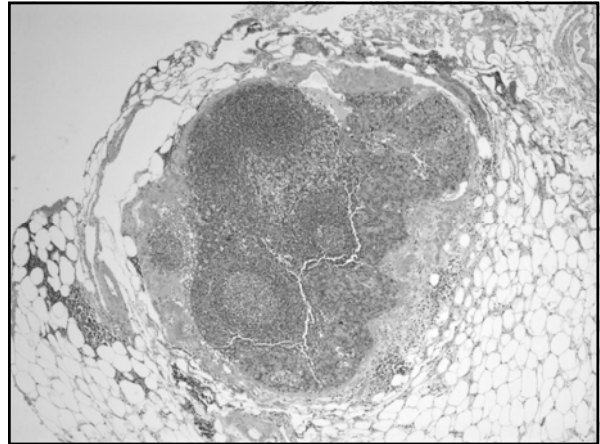
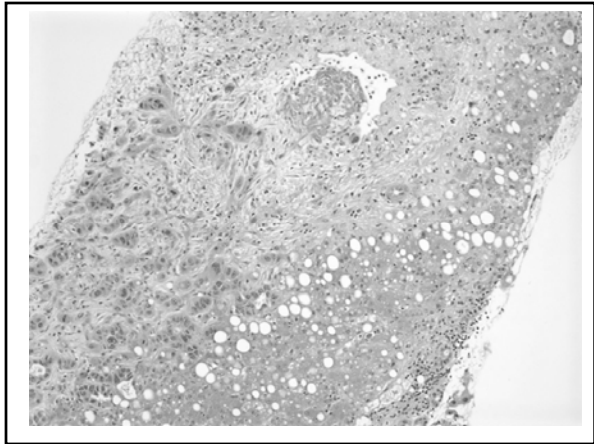
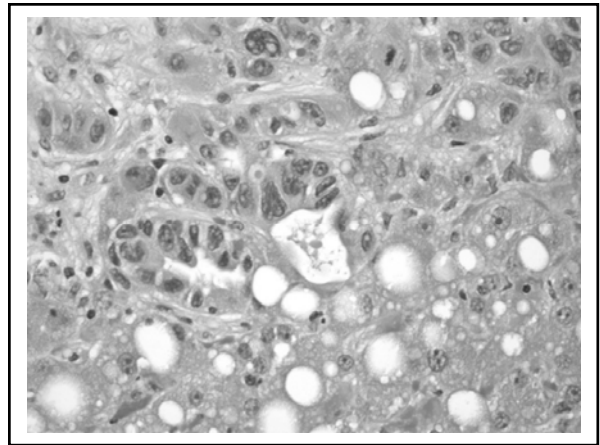
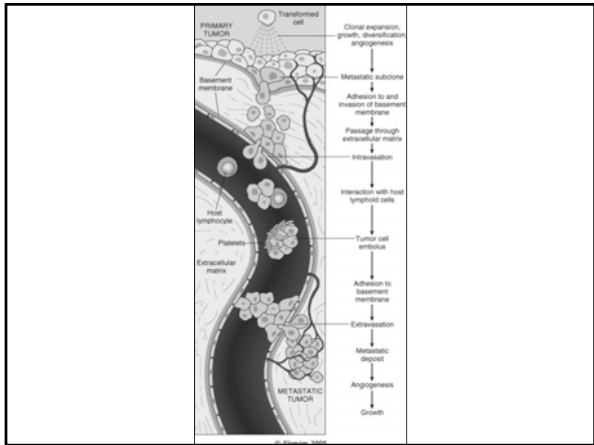
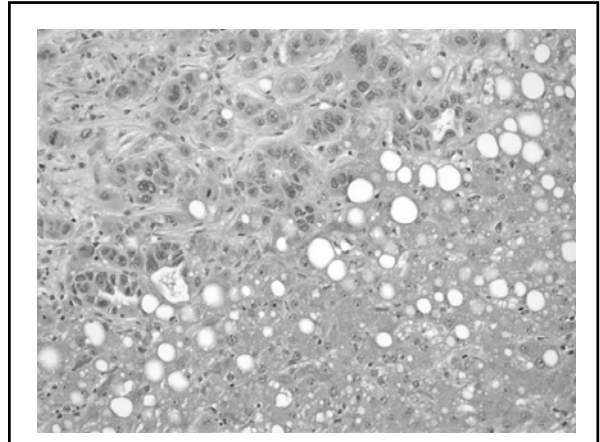
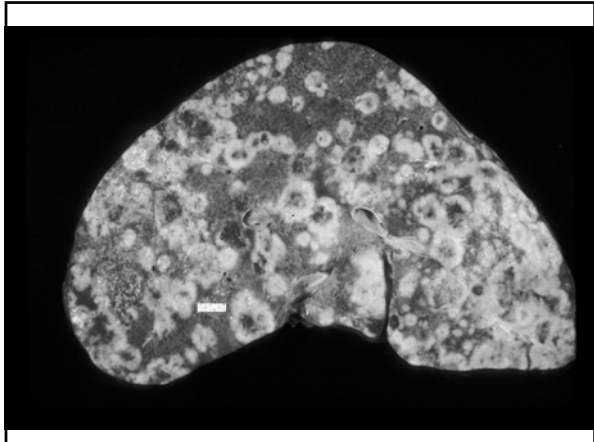


**Steps of Successful Metastasis**

- **Detachment of tumor cells** (E-cadherin loss)
- **Degradation of ECM** (MMP's - overexpressed and TIMP's - reduced)
- **Attachment to new ECM proteins** (cleavage products of collagen and laminin bind to receptors on tumor cells - stimulate migration)
- **Migration of tumor cells** (cytokines from tumor cells direct movement, autocrine, and stromal cells produce paracrine effectors, HGF/SCF, for motility that bind to tumor cells)



- Homing of Tumor Cells**
- Most metastases predicted by vascular and lymphatic drainage
  - Some homing related to expression of endothelial adhesion molecules
  - **Chemokines and chemokine receptors** are also involved in homing. (breast ca cells-chemokine receptors: CXCR-4 and -7 bind to the chemokines CXCL12 and CCL21 on distant organs)
  - After extravasation, tumor cells survive only in receptive ECM and stroma



### Cinical Aspects of Neoplasia

1. Epidemiology:

Cancer incidence—Cancer deaths

2. Pathogenetic factors: a balance of risks

3. Clinical effects of cancer

4. Death in cancer

5. Grading and Staging

6. Diagnosis

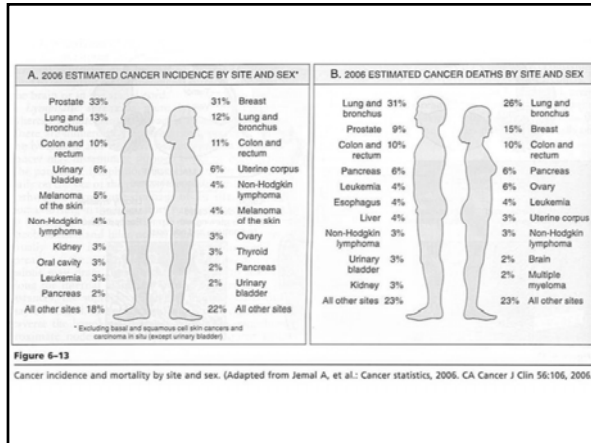
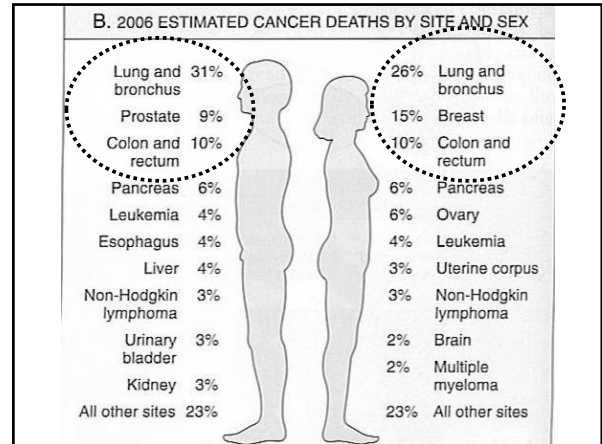
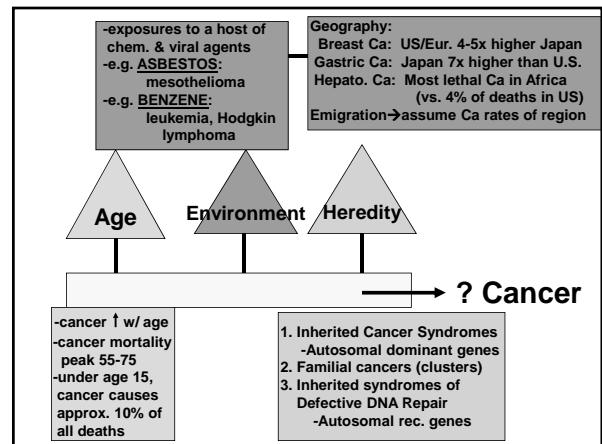
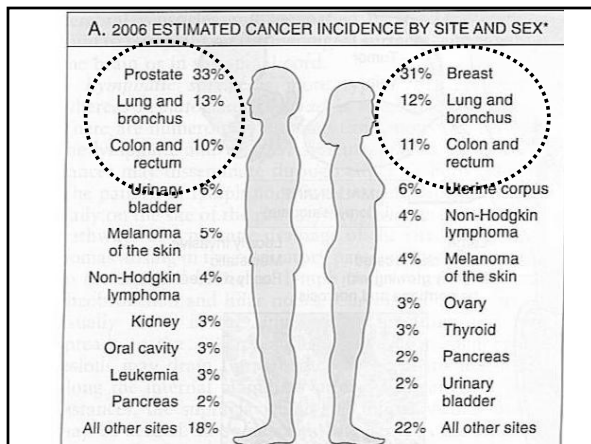
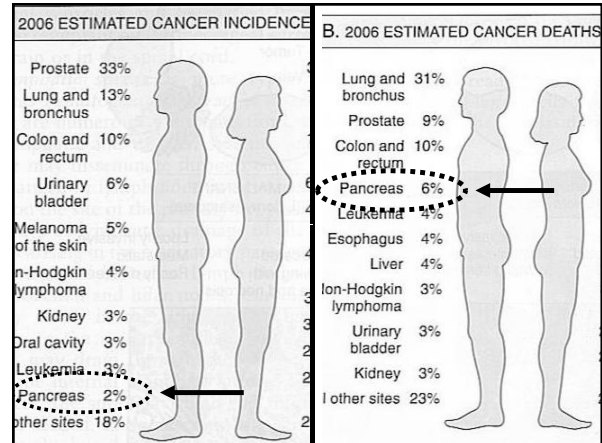


Figure 6-13 Cancer incidence and mortality by site and sex. (Adapted from Jemal A, et al.: Cancer statistics, 2006. CA Cancer J Clin 56:106, 2006.)

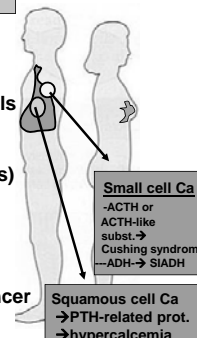




**Table 6-3 Inherited Predisposition to Cancer**

Inherited Cancer Syndromes (Autosomal Dominant)	
Gene	Inherited Predisposition
<i>RB</i>	Retinoblastoma
<i>p53</i>	Li-Fraumeni syndrome (various tumors)
<i>p16INK4A</i>	Melanoma
<i>APC</i>	Familial adenomatous polyposis/colon cancer
<i>NF1, NF2</i>	Neurofibromatosis 1 and 2
<i>BRCA1, BRCA2</i>	Breast and ovarian tumors
<i>MEN1, RET</i>	Multiple endocrine neoplasia 1 and 2
<i>MSH2, MLH1, MSH6</i>	Hereditary nonpolyposis colon cancer
<i>PATCH</i>	Nevoid basal cell carcinoma syndrome

**Clinical Effects of Cancer**



- 1. Cachexia**
  - cytokines → anorexia
  - TNF:** from macrophages/tumor cells
  - suppresses appetite
  - inhibits lipoprotein lipase (inhibits FFA release from lipoprot's)
  - Proteolysis-inducing factor:**
  - breaks down skeletal muscle
- 2. Paraneoplastic syndromes**
  - hormone production by tumor cells
  - present in 10% - 15% of pts. with cancer
- 3. Venous thrombosis**
  - mucins from Ca's activate clotting
  - e.g. Pancreas: Trousseau phenomenon

**Small cell Ca**  
 -ACTH or ACTH-like subst. → Cushing syndrome  
 -ADH → SIADH

**Squamous cell Ca**  
 → PTH-related prot. → hypercalcemia

**Familial Cancers**

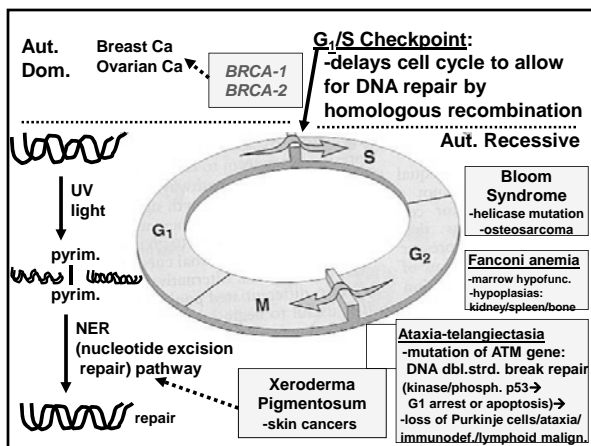
Familial clustering of cases, but role of inherited predisposition not clear for each individual

- Breast cancer (not linked to BRCA1 or BRCA2)
- Ovarian cancer
- Pancreatic cancer

**Inherited Autosomal Recessive Syndromes of Defective DNA Repair**

- Xeroderma pigmentosum
- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi anemia

- Death in Cancer**
- 1. Overwhelm organ function**
    - liver: ↓ coagulation, other protein synthesis
    - lung: ↓ diffusion/oxygenation
    - pancreas: biliary obstruction/liver mets → anorexia
  - 2. Pulmonary embolus** (pro-thrombotic Ca's)
  - 3. Progressive somnolence:** hypercalcemia, etc.
  - 4. Systemic electrolyte imbalances:**
    - cardiac arrhythmia
    - ↓ mentation
  - 5. Tumor-related products:**
    - depression/other CNS effects



- Diagnosis of Cancer**
- History—physical—occupation—exposure
  - Radiology
  - Blood tests: tumor markers
  - Morphologic Diagnosis
    - light microscopy: biopsy
    - cytology (Fine Needle Aspiration—FNA)
    - immunohistochemistry
    - fluorescence *in situ* hybridization (FISH)
    - molecular probes, incl. gene microarray
    - flow cytometry (lymphomas, leukemias)

### Tumor Markers

**\*Molecules in plasma produced by tumor cells**

**Oncofetal antigens**

gut  
yolk sac, liver

**carcinoembryonic antigen (CEA)**

colon Ca; pancreas, lung, breast Ca

**alphafetoprotein (AFP)**

hepatocellular Ca, germ cell testis Ca

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**Specific proteins**

**PSA (prostatic specific antigen)**

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**Mucins & other glycoproteins: CA's: carbohydrate antigens**

CA-125  
ovary

CA-19-9  
bile ducts, panc.

CA-15-3  
breast

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**Hormones**

trophoblastic tumor (placenta)

testis

**HCG**

medullary Ca  
thyroid

**calcitonin**

**Table 2. Frequency of high epidermal growth factor receptor (EGFR) expression in lung cancer by histologic characterization**

Histology	EGFR expression, % (n)
Small cell	0 (19)
Adenocarcinoma	65 (563)
Large cell	68 (72)
Squamous	84 (754)

Reprinted from Bunn PA Jr, Franklin W. Epidermal growth factor receptor expression, signal pathway, and inhibitors in non-small cell lung cancer. *Semin Oncol* 2002;29(suppl 14):38-44, with permission from Elsevier.

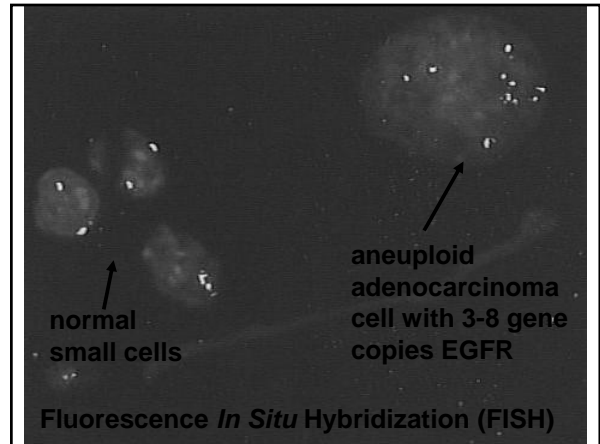
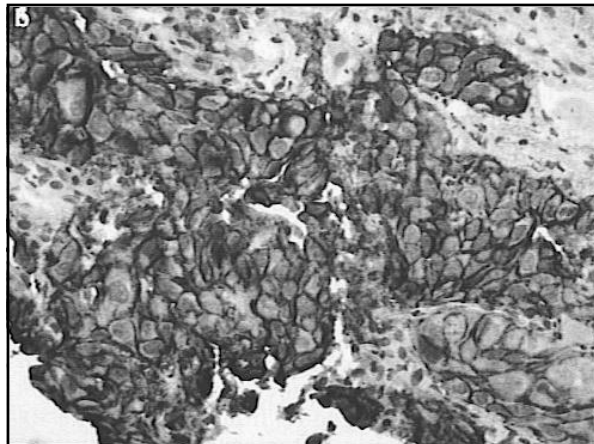
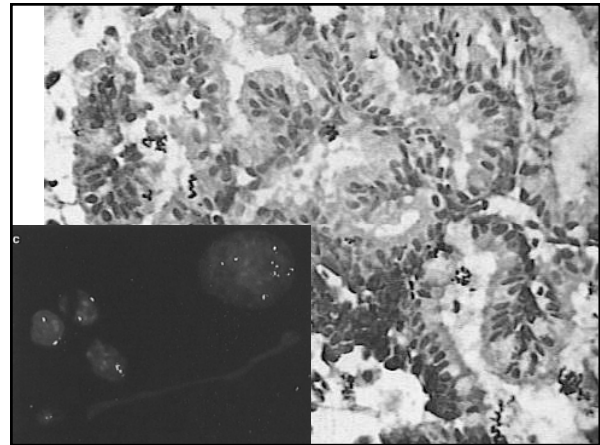
**Immunohistochemistry:**  
--monoclonal Ab to specific cell Ag's

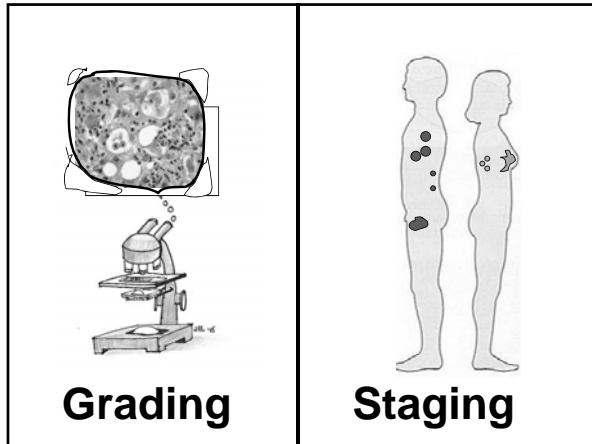
CK7+  
CK20-

CK7-  
CK20-

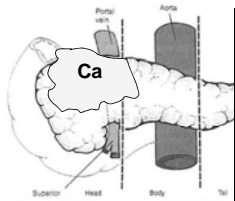
CK7-  
CK20+

Cytokeratins in epith. cells:  
**CK7 and CK20**





**Staging: TNM  
AJC (American Joint Committee)**



**DEFINITION OF TNM**

**Primary Tumor (T)**

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma *in situ*\*
- T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

STAGE GROUPING		AJC	
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

**Regional Lymph Nodes (N)**

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

**Distant Metastasis (M)**

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis