Neoplasia

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Definitions

- **Neoplasia:** new growth
- **Oncology**: **Onco**: tumor, **logos**: study of
- Neoplasm is benign and malignant
- **Cancer** is a malignant neoplasm
- **Invasive**: tumor capable of destroying structures
- **Metastasis**: spread to distant sites

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Definitions

- **Growth**: Increase in size due to synthesis of tissue components
- **Proliferatation**: Cell division
- **Differentiation**: Functional and structural maturity of cells
- **Tumor**: Swelling / new growth / mass

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Controls of Growth

- **Growth factors** – PDGF, FGF
- **Growth Inhibitors**.
- **Cyclins**, Cyclin dependent kinases (CDK).
- **Cancer suppressor genes** – p53
- **Oncogenes** – c-onc, p-onc, v-onc etc.

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Non-Neoplastic Proliferation

Controlled & Reversible

- **Hypertrophy –** increase in cell size
- **Hyperplasia –** increase in cell number
- **Metaplasia –** change of cells type
- **Dysplasia –** disordered cells

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Neoplastic Proliferation

Uncontrolled & Irreversible

- **Progressive**, **purposeless, pathologic, proliferation** of cells characterized by **loss of control** over cell division.
- **DNA damage** at growth control genes is central to development of neoplasm.

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How do we get cancer

- Damage to genetic material
- Affects different sites in the genome
- Evolution of more aggressive clones

Carcinogens (Chemical, radiation, viruses)
↓
DNA damage
↓
Neoplasm

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Neoplasm definition:

"an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change"

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Neoplasm Properties

- **Normal properties loss:**
  - Increased proliferation
  - Decreased cell death
  - Failure to differentiate
- **Abnormal properties develop:**
  - Invasion
  - Metastasis

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Tumors have two basic components:

1) Parenchyma:

- made up of neoplastic cells
- from which the tumor derives its name

2) Stroma:

- supporting, host-derived, non-neoplastic
- made up of connective tissue and blood vessels
- provides support for the growth of parenchyma
- crucial to the growth of the neoplasm

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The classification of neoplasm

1. **Behaviour-** benign and malignant
2. **Extent of spread-** Primary and secondary
3. **The cell of origin or histogenesis:**
   - epithelial
   - mesodermal/connective tissue
   - hematopoietic
   - nervous system
   - germ cells
   - embryonic tissue

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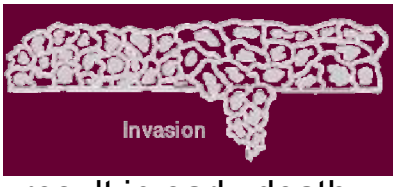
Neoplastic Behaviour

- The terms “benign” and “malignant” describe the biologic or clinical behavior of a tumor.
- **Benign:**
  - **Localized, non-invasive,** patient usually survives
- **Malignant (Cancer):**
  - **Spreading, Invasive,** may result in early death of the patient



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The main distinguishing features of benign and malignant neoplasms

BENIGN	MALIGNANT
Small size	Large size
May be encapsulated	Not encapsulated
Well circumscribed	Poorly circumscribed
Well differentiated tissues	Loss of differentiation
Cell retain normal functions	Cells lose normal functions
No invasion	Invasion of normal tissue
No necrosis	Necrosis
Few mitoses	Many mitoses
Non-lethal	Potentially lethal
Non metastasising	Metastasising
Suffix "oma" eg. Fibroma.	Suffix "Carcinoma" or "Sarcoma"

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Extent of spread

- **Primary tumour** gives rise to **secondary tumours**
- Tumours invade lymphatics, blood vessels or through peritoneal or other surfaces to form secondaries (metastases)
- Always think the tumour might have a primary tumour elsewhere

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Origin of Neoplasm

- Epithelial
- Mesodermal/connective tissue
- hematopoietic
- nervous system
- germ cells
- embryonic tissue

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Nomenclature: Cell of origin + Suffix

Tissue of Origin	Benign	Malignant
Epithelial:		
• Squamous	Papilloma	Squamous cell *carcinoma*
• Transitional	Papilloma	Transitional cell *carcinoma*
• Glandular	Adenoma	Adeno*carcinoma*
Connective Tissue/mesenchymal:		
• Fibrous tissue	Fibroma	Fibrosarcoma
• Fat	Lipoma	Liposarcoma
• Bone	Osteoma	Osteosarcoma
• Cartilage	Chrondroma	Chrondrosarcoma
• Smooth muscle	Leiomyoma	Leiomyosarcoma
• Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
• Blood vessels	Hemangioma	Angiosarcoma

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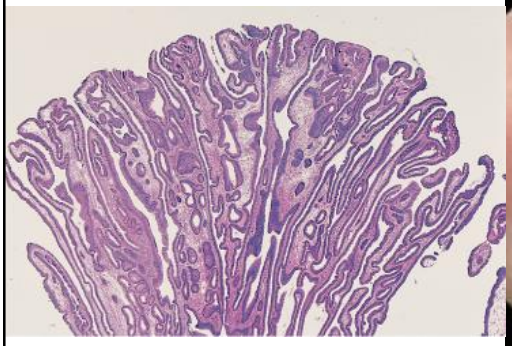
Papilloma is a benign neoplasm growing on any surface, composed of epithelial cells forming finger like projections.



Papilloma in esophagus

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Adenoma:

- Applied to benign epithelial neoplasms producing gland patterns.

  E.g. Surface epithelium (stomach, small intestine & colon)

- Applied to benign neoplasms derived from glands but not necessarily exhibiting gland patterns.

  E.g. Solid glandular epithelium (endocrine and exocrine) **and ducts** (Thyroid, kidney, liver)

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Examples of malignant tumors

- **Sarcoma (mesenchymal derivation):**
  - fibrosarcoma
  - chondrosarcoma
- **Carcinoma (epithelial derivation):**
  - adenocarcinoma,
  - squamous cell carcinoma

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Exceptions in Terminology

Malignant tumors:

Hematopoietic

- Leukemias
- Lymphomas

Brain tumors

- Glioma

Germ cell tumor

- Teratoma
- Seminoma

Pediatric tumors

- Hepatoblastoma
- Nephroblastoma
- Retinoblastoma

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Characteristics of benign & malignant neoplasms

Tumors can be distinguished by:

1. **Differentiation and anaplasia**
2. **Rate of growth**
3. **Local invasion**
4. **Metastasis**

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1. Differentiation & Anaplasia

Differentiation: extent to which **parenchymal** neoplastic cells resemble normal cells morphologically and functionally, while **stroma** does not aid in the separation of benign from malignant.

- **Well-differentiated tumors:**
  contain cells that resemble the normal cells of origin and retains its functional capacity
- **Poorly-differentiated or undifferentiated tumors:**
  contain cells that do not resemble their normal cells of origin

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Differentiation & Anaplasia

- **Benign tumors** are composed of well-differentiated cells.
- **Malignant tumors** are characterized by a wide range of cellular differentiation (well, moderate, poor, **undifferentiated**).
- **Anaplasia:** malignant neoplasms that are composed of **undifferentiated** cells
- **Undifferentiated:** loss of the structural and functional differentiation of normal cells.

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Anaplasia: lack of differentiation

Histological Features of anaplasia:

- Cellular pleomorphism
- Giant cells
- Hyperchromatic nuclei
- Nuclear- cytoplasmic ratio may approach 1:1
- Nuclear pleomorphism
- Mitosis is numerous and/or atypical
- Loss of cell polarity

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Dysplasia: "disordered growth"

- **Dysplasia** is a non-neoplastic proliferation
- **Dysplasia** is an abnormal type of excessive cell proliferation characterized by loss of normal tissue arrangement and cell structure in epithelium.
- **Dysplasia** may or may not progress to cancer.
- **In epithelia**, represents a state between hyperplasia and carcinoma in situ (pre-invasive neoplasia)
- Pleomorphism & mitoses are more prominent than in the normal

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2. Rate of growth

- Benign and well-differentiated malignant tumors have a slower rate of growth than moderately-differentiated and poorly-differentiated malignant tumors.
- There are exceptions.
- Malignant tumors sometimes grow slowly for years and suddenly enter a phase of rapid growth

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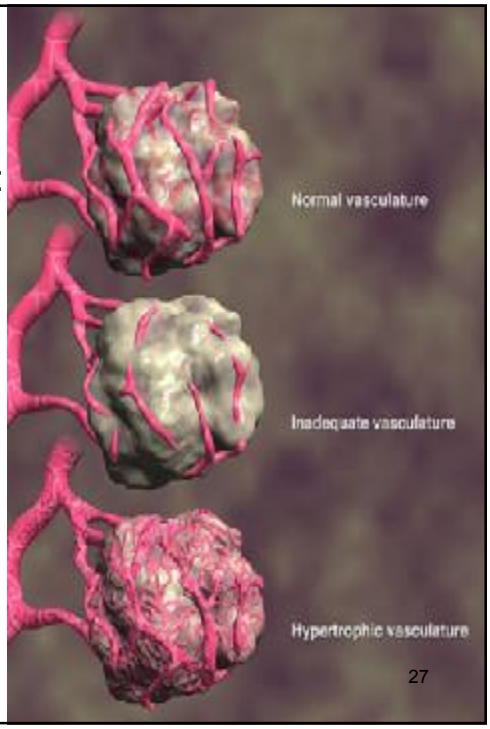
Rate of Growth

- **Factors that can affect the growth rateof tumor**:
  - Blood supply
  - Site
  - hormonal stimulation
- **Example**:

Leiomyomas: influenced by estrogen, increase during pregnancy, and cease growing or atrophy after menopause



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3. Invasion

- **Benign tumors**
  - usually grow by slow expansion
  - **usually** encapsulated
- **Malignant tumors** (cancer)
  - usually infiltrate and destroy surrounding tissue
  - do not develop well-defined capsules
  - Some induce formation of dense fibrous stroma (desmoplasia)
  - Pathologists carefully examine the margin of resected specimens *(clean margins).*

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4. Metastasis

- **Definition**: the development of secondary implants (metastases) discontinuous with the primary tumor, possibly in distant tissues
- Next to metastases, local invasiveness is the most reliable feature that distinguishes malignant from benign tumors.
- Not all cancers have equivalent ability to metastasize, e.g Basal cell carcinoma

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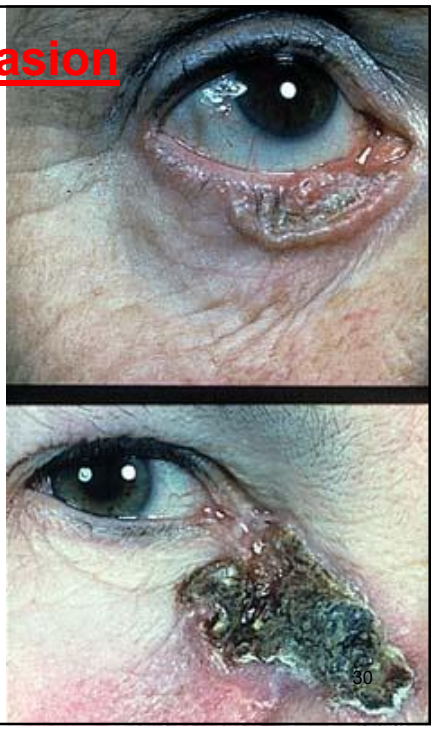
Malignant tumors: Invasion

Basal cell carcinoma (BCC): skin cancer that is common and slow growing. Grossly, the tumor begins as papules with rolled margins (top photo), but can ulcerate and locally invade underlying structures and bone (bottom photo). Hence, the name "**rodent ulcer**."



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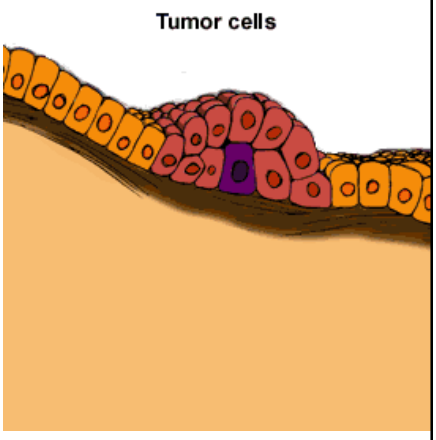
4. Metastasis

- **Metastasis** indicates malignancy
- ~ 30% of newly diagnosed patients with solid tumors present with clinically evident metastases.
- In general, the more anaplastic and the larger the primary neoplasm, the more likely is metastatic spread; however, with exceptions.



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Methods of spread

1. **Direct Spread**
2. **Seeding of body cavities**: ovarian tumors
3. **Hematogenous spread**: favored pathway for sarcomas. The liver and lung are the most frequently involved secondary sites.
4. **Lymphatic spread**: is more typical of carcinomas

Metastasis

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Biology of Invasion and Metastasis

- Invasion of the basement membrane
- Movement through extracellular matrix
- Penetration of vascular or lymphatic channels
- Survival and arrest within the circulating blood or lymph
- Exit from the circulation into new site
- Survival and growth as a metastasis

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Seeding of body cavities

- Occurs when neoplasms invade a natural body cavity.
- **Examples:**
  - **Carcinoma of the colon** may penetrate the wall of the gut and reimplant at distant sites in the peritoneal cavity.
  - **Lung cancers** in the pleural cavities.
  - **Cancers of the ovary** in the peritoneal cavity.

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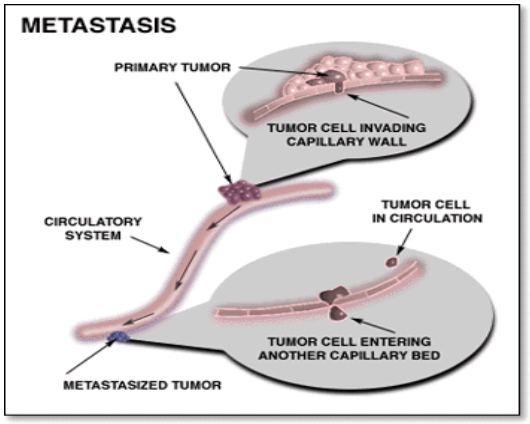
Hematogenous spread:

- It is the most feared consequence of a cancer.
- **It is the favored pathway for sarcomas**
- arteries are penetrated less than veins.
- **Liver & lungs** are the most frequently involved secondary sites



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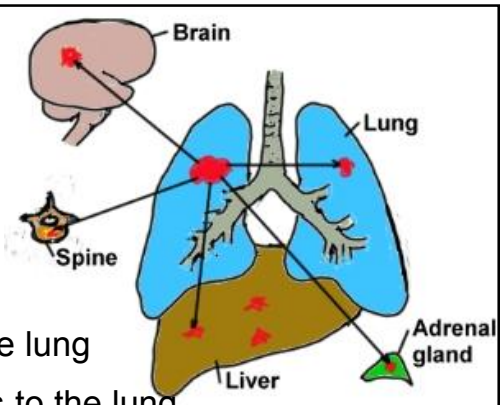
Hematogenous Spread



Examples:

- Renal cell carcinoma to the lung
- Hepatocellular carcinomas to the lung
- Colon cancer to the liver
- Prostatic carcinoma preferentially spreads to bone
- Bronchogenic carcinomas to the adrenals and the brain
- Neuroblastomas spread to the liver and bone

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Lymphatic spread

- It is more typical of carcinomas
- **Example:** Lung and breast carcinoma
- **Skip metastases:**
  - The cancer cells seem to traverse the lymphatic channels within the immediately proximate nodes to be trapped in subsequent lymph nodes
  - The cells may traverse all of the lymph nodes to reach the blood via the thoracic duct.
- The necrotic products of the neoplasm and tumor antigens often evoke reactive changes in the nodes:
  - Lymphadenitis
  - Sinus histiocytosis

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Grading & Staging of Tumor

- **Grading** (Microscopic)
  - Indicates how aggressive it is
  - How much different it looks from the tissue of origin
- **Staging** (clinical)
  - How advanced the cancer is
  - How far it has spread

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Grading & Staging

- **Grading** is based on the microscopic features of the cells which compose a tumor and is specific for the tumor type.
- **Staging** is based on clinical, radiological, and surgical criteria, such as, tumor size, involvement of regional lymph nodes, and presence of metastases. Staging usually has prognostic value.

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Grading of Tumor

- **Malignant neoplasms**
  - **Low grade**, is relatively non-aggressive
  - **high grade**, likely to grow and spread quickly.
- **Features used to grade malignant neoplasms:**
  1. Degree of tissue differentiation.
  2. Number of mitoses.
  3. Host response in terms of lymphocytic infiltration.
  4. Invasive margin of the tumor.
  5. Degree of nuclear pleomorphism

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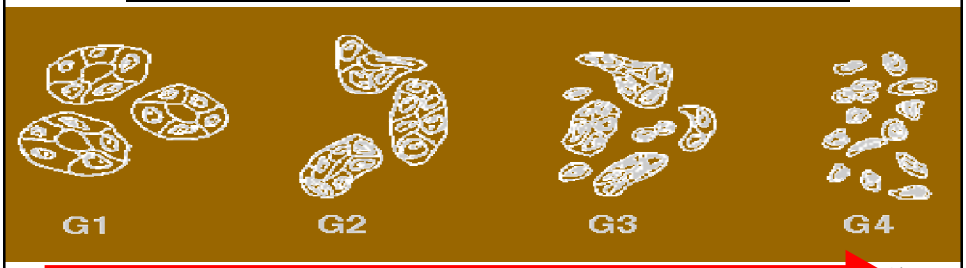
Grading of tumours

GRADE	
1	Well differentiated
2	Moderately differentiated
3	Poorly differentiated
4	Undifferentiated (anaplastic)



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Near normal Undifferentiated

Why do we grade & stage cancer?

- To estimate the prognosis
  - i.e. how long the patient may survive
- To decide how to treat the tumor
  - More advanced/ aggressive tumors are given more radical treatment
- To compare treatments or prognostic factors in research
  - Do males die earlier of a certain tumour than females?

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Tumours are staged using TNM system

- Each organ has a different system
- **Three components are included**:
  - **T** Extent of primary **T**umour
  - **N** Regional lymph **N**ode metastasis
  - **M** Distant **M**etastases
- An overall **stage** is allocated I to IV

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T staging of breast cancer

T stage	
Tis	In situ disease
T1	< 2cm
T2	2 – 5 cm
T3	> 5cm
T4	Involving skin or chest wall

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N & M staging of breast cancer

N stage	
N0	No nodes
N1	Ipsilateral nodes
N2	Contralateral nodes
M stage	
M0	No distant mets
M1	Distant mets

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Other staging systems

- The **Dukes staging** system for colorectal cancer
- **Four stages**
  - **A** Confined to bowel wall
  - **B** Through bowel wall
  - **C** Regional lymph node metastases
  - **D** Distant metastases

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Epidemiology

- **Cause**: contributes to understanding the association of cancer with certain **causastive agents** (smoking), or with **races** (stomach cancer in Japan)
- **Geography**: comparison of colon cancer incidence between Western world and Africa led to recognition of the role of diet (colon cancer)
- **Prevention**: underscores the importance of **screening** in controlling cancer (cervix, breast, colon)

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Some causative factors associated with cancer at various sites

Smoking	Mouth, pharynx, oesophagus, lip, larynx, lung, bladder
Alcohol	Mouth, pharynx, larynx, oesophagus, colorectal
Iatrogenic:	
• Estrogens	Endometrium, vagina, breast
• Androgens	Prostate
• Radiotherapy	carcinoma of breast & Bronchus

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Some causative factors associated with cancer at various sites

High-fat diet	Breast cancer
Hepatitis B virus	Liver (hepatocellular carcinoma)
Hepatitis C virus	Liver (hepatocellular carcinoma)
Epstein–Barr virus	Burkitt's lymphoma Hodgkin's lymphoma
Helicobacter pylori	Stomach (gastric cancer)

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Environmental Carcinogens

- **Drugs:** immune suppressing etc..
- **Organic chemicals:** Insecticides, herbicides, etc..
- **Cigarette Smoke**
- **Ethanol**
- **Heavy Metals**
- **Sexually transmitted viruses:** Herpes simplex, Human papilloma virus
- **Radiation:** Ultraviolet light

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Heredity and Cancer

Inherited Cancer Syndromes:

- **Autosomal Dominant**
- **Autosomal Recessive Syndromes**
- **Familial Cancers**

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Table 7–5. INHERITED PREDISPOSITION TO CANCER

Inherited Cancer Syndromes (Autosomal Dominant)
Inherited predisposition indicated by strong family history of uncommon cancer and/or associated marker phenotype
- Familial retinoblastoma **(40% are familial, usually bilaterally)**
- Familial adenomatous polyps of the colon
- Multiple endocrine neoplasia syndromes
- Neurofibromatosis types 1 and 2
- Von Hippel–Lindau syndrome

Familial Cancers
Evident familial clustering of cancer but role of inherited predisposition may not be clear in an individual case
- Breast cancer
- Ovarian cancer
- Colon cancers other than familial adenomatous polyps

Autosomal Recessive Syndromes of Defective DNA Repair
- Xeroderma pigmentosum
- Ataxia-telangiectasia
- Bloom's syndrome
- Fanconi's anemia

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Familial Cancers

- Examples: 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
  - sometimes multiple or bilateral tumors
- Familial cancers are not associated with specific marker phenotypes, e.g. The transmission pattern is not clear.
- certain familial cancers can be linked to the inheritance of mutant genes. Examples include linkage of BRCA1 and BRCA2 genes to familial breast and ovarian cancers.

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Acquired Preneoplastic Disorders

- **Regenerative** (e.g. hepatocellular carcinoma in cirrhosis)
- **Hyperplastic** (e.g. endometrial carcinoma in endometrial hyperplasia)
- **Dysplastic** (e.g. Lung cancer in bronchial dysplasia)
- **Atrophic** (e.g. gastric carcinoma in atrophic gastritis)
- **Ulcerative** (e.g. colorectal carcinoma in ulcerative colitis)

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Clinical Features of Neoplasia

The prognosis of a patient with any type of neoplasm depends on:

- **rate of growth of the tumor**
- **tumor size**
- **tumor site**
- **cell type and degree of differentiation**
- **presence of metastasis**
- **responsiveness to therapy**
- **general health of the patient**

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Clinical Features of Neoplasia

- **Local effect**
  - Pressure effect
  - Functional activity (e.g. hormone synthesis)
  - Bleeding
  - Infection
- Cachexia (wasting)
- Paraneoplastic syndromes

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Cachexia (wasting syndrome)

- **Definition**: loss of body fat and body mass associated with weakness, anorexia, and anemia
- Often correlates with tumor size and extent of metastases
- **Origin of cancer cachexia is multifactorial**:
  - reduced calorie intake due to loss of appetite
  - increase in basal metabolic rate
  - central effects of tumor on hypothalamus, probably related to macrophage production of TNF & IL-1

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Paraneoplastic Syndromes

- **Definition**: Symptoms other than cachexia that cannot be explained by local or distant spread of the tumor

  They appear in 10-15% of patients with cancer
- **Most common ones:** hypercalcemia, Cushing syndrome, and nonbacterial thrombotic endocarditis
- **Often associated with the following neoplasms:**

  bronchogenic and breast cancers and hematologic malignancies

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Paraneoplastic Syndromes

- Endocrinopathies
- Neuromyopathies
- Osteochondral Disorders
- Vascular Phenomena
- Fever
- Nephrotic Syndrome

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Paraneoplastic syndromes		
Syndrome	**Mechanism**	**Example**
Cushing's Syndrome	ACTH-like substance	Lung (oat cell) carcinoma
Hypercalcemia	PTH-like substance	Lung (squamous cell) carcinoma
Hyponatremia	Inappropriate ADH secretion	Lung (oat cell) carcinoma
Polycythemia	Erythropoietin-like substance	Renal cell carcinoma
Trousseau's Syndrome	Hypercoagulable state	Various carcinomas
Hypoglycemia	Insulin-like substance	Various carcinomas and sarcomas
Carcinoid Syndrome	Seretonin, bradykinin	Metastatic malignant carcinoid tumors

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Paraneoplastic Syndromes: **Endocrinopathies**

- **Hypercalcemia** (Cancer is the most common cause of hypercalcemia
- **Causes of hypercalcemia in cancer:**
- **Hormonal** (e.g. PTHrP synthesis in squamous cell lung carcinomas)
- **Osteolytic metastatic disease** of bone (e.g. metastatic breast carcinoma)
- **Tumor-derived factors** (e.g. TGF-α, that activates osteoclasts and the active form of vitamin D)

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Paraneoplastic Syndromes: **Endocrinopathies**

- **Hypoglycemia** - caused by tumor over-production of insulin or insulin like activities
  - Fibrosarcoma, Cerebellar hemangioma, Hepatocarcinoma
- **Carcinoid syndrome** - Caused by serotonin and bradykinin produced by the tumor
  - Bronchial carcinoids, Pancreatic carcinoma, Carcinoid tumors of the bowel

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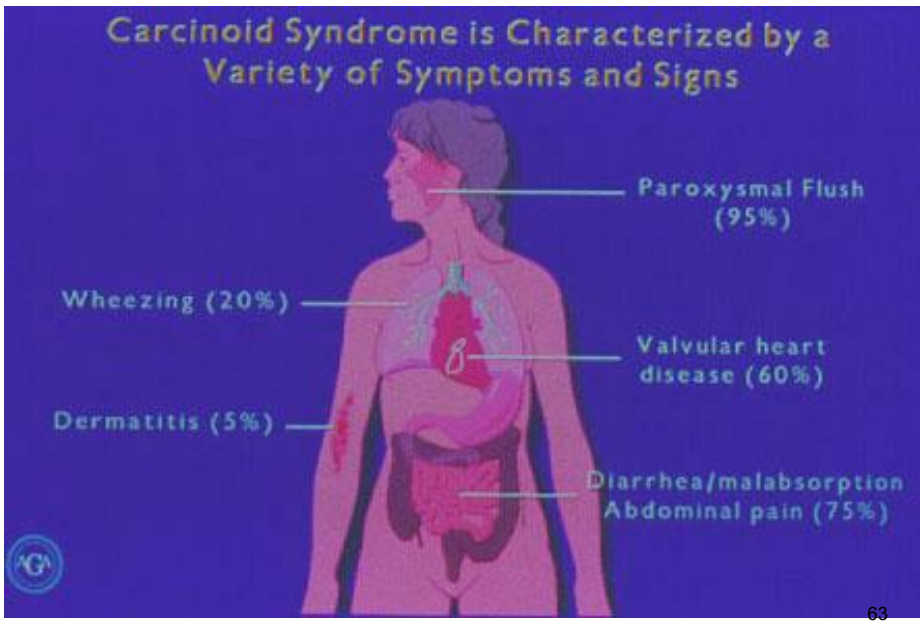

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Paraneoplastic Syndromes: **Endocrinopathies**

- **Polycythemia** - caused by tumor production of erythropoietins
  - Renal cell carcinoma, Cerebellar hemangioma, Hepatocarcinoma
- **WDHA syndrome** (watery diarrhea, hypokalemia, and achlorhydria) - caused by tumor production of vasoactive intestinal polypeptide (VIP).
  - Islet cell tumors, Intestinal carcinoid tumors

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Paraneoplastic Syndromes

Neuromyopathies:

- **Myasthenia** - A block in neuromuscular transmission possibly caused by host antibodies against the tumor cells

(e.g. Bronchogenic carcinoma)

Osteochondral Disorders

- **Hypertrophic osteoarthropathy** and **clubbing** of the fingers

(e.g. Bronchogenic carcinoma)

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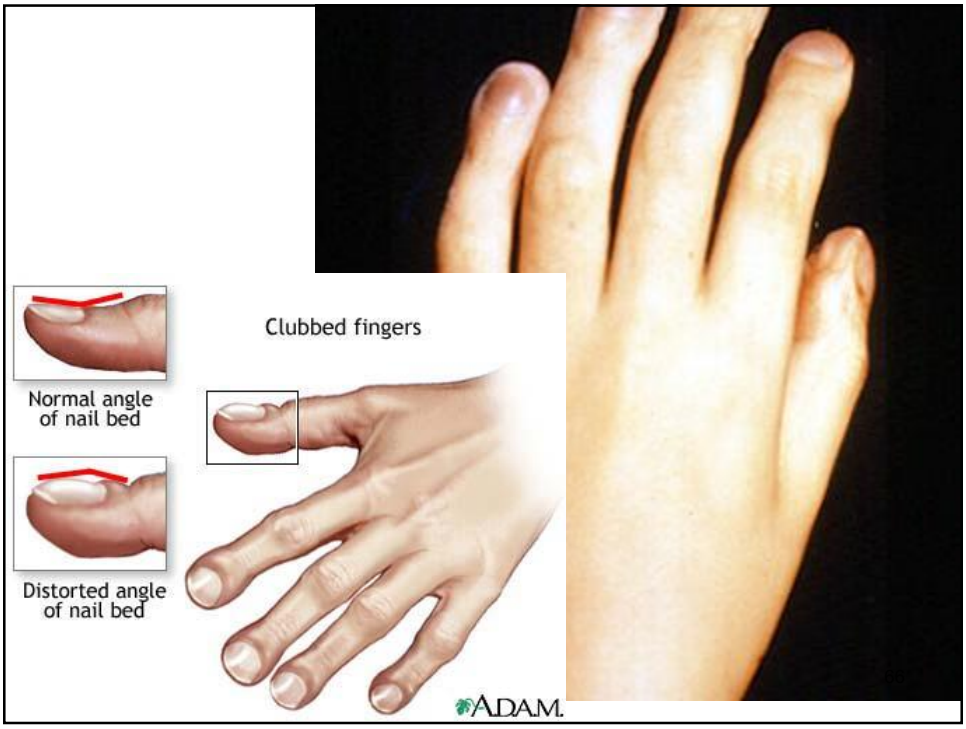

Paraneoplastic Syndromes

Vascular & hematoligical changes

- **Hyper-coagulability** leading to:
  - **venous thrombosis** (Trousseau's phenomenon)

    e.g.Pancreatic and bronchogenic carcinomas
  - **nonbacterial thrombotic endocarditis**

    e.g. sterile vegetations on valves that occur with advanced carcinomas.
- **Anemia** (e.g. Thymic neoplasms)

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Paraneoplastic Syndromes

Fever

- **Associated with bacterial infections**
  - Common where blockage of drainage occurs
- **Not associated with infection**
  - Likely caused by response to necrotic tumor cells and/or immune response to necrotic tumor proteins.

Nephrotic Syndrome

- probably caused by damage to renal glomeruli by tumor antigen-antibody complexes.

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What Are The Final Complications Of Malignancy (Causes Of Death)

- metastases
- cachexia
- severe anemia, throbocytopeina
- hypercoagulability
- rupture into major vessels e.g. bleeding
- compression of vital organs
- organ failure e.g. renal failure
- infection e.g. pneumonia

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Tumor Diagnosis

- **History and Clinical examination**
- **Imaging** - X-Ray, US, CT, MRI
- **Tumor markers-** laboratory analysis
- **Cytology** –Pap smear, FNAB
- **Biopsy** - Histopathology.
- **Molecular Tech** – Gene detection.

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Tumor Diagnosis

- **Immunohistochemistry**
- **Flow cytometry**
- **Electron microscopy**
- **In Situ Hybridization**

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Tumor markers: sometimes diagnostic or prognostic

Some serological markers associated with malignant tumors:

hCG	choriocarcinoma
AFP	hepatocellular ca
calcitonin	thyroid medullary ca
prolactin	pituitary adenomas
CA 125	ovarian carcinoma
PSA	prostate carcinoma

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Molecular Basis of Cancer

- **Four classes of genes are targets of genetic damage:**
  1. The growth promoting **proto-oncogenes**
  2. The growth-inhibiting **tumor-suppressor genes** (**anti-oncogenes**)
  3. Genes that regulate apoptosis
  4. The DNA repair genes

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Mechanisms of carcinogenesis

Cancer as a multistep process:

1. **Initiation**: DNA alteration or cell change
2. **Tumor-promotion**: from single mutated cell to formation of tumor
3. **Tumor-progression**: development of malignancy

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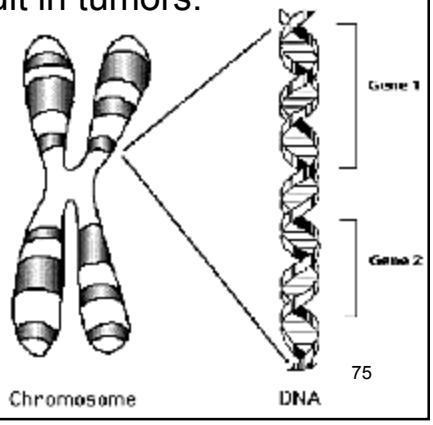
Step 1: Initiation

- Results from mutation of DNA to **activate a proto-oncogene** or **inactivate a tumor suppressor gene**.
- Initiation alone does not result in tumors.

Some initiators can subsequently act as promoters (are "**complete carcinogens**").



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Step 2: Promotion

- **Promotors** are usually substances that **produce cell activation and proliferation**.
- Effects of promotors are reversible.
- **Promotors cannot induce neoplasia:**

  i) alone

  ii) if applied before initiator

  iii) if applied in too small amount

  iv) if too much time elapses between applications

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Step 2: Promotion

The promoter does not cause mutation, but it leads to clonal expansion of the initiated (mutated) cells.

Promoters: e.g. hormones (estrogen), growth factors

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Step 3: Progression

- **Karyotypic instability:**
  - Increased growth rates
  - Increased invasiveness
  - Increased hormonal response
  - Anaplasia

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Step 3: Progression

- Every Cancer analyzed reveals **multiple genetic alterations** involving activation of several oncogenes and loss of two or more cancer suppressor genes.
- **The good example is colon cancer:**
  - Colon epithelial hyperplasia
  - Formation of adenomas
  - Malignant transformation

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Karyotypic Changes in Tumors

- Point mutation: e.g. ras oncogene
- Balanced translocations
- Gene amplification
- Deletions
- Whole chromosomes may be gained or lost.

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Molecular Basis of Multistep Mechanism

Special order of the mutations is important

- Genes that regulate entry of cells into the multi-step carcinogenesis are called **gatekeepers**
  - **E.g.** mutations of Rb, NF-1, VHL, or APC gives rise to retinoblastoma, schwannomas, renal cell cancer, and colon cancer
- In contrast to gatekeeper genes, those that affect genomic stability are called **caretaker** genes
  - **E.g.** the DNA repair genes

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Carcinogens

Genetic damage may be:

1. **Inherited:**
2. **Acquired**:
   a) Chemical agents
      - Direct agents
      - Indirect agents
   b) Radiations
   c) Microbial agents (viruses)

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A) Chemical Carcinogens

- **Direct agents:**

  They require no metabolic conversion to become carcinogenic

- **Indirect agents:**

  They become active after metabolic conversion

- These agents react with RNA, cellular proteins, and DNA
- Some chemical carcinogens are augmented by certain agents that are called promoters

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MAJOR CHEMICAL CARCINOGENS

Direct-Acting Carcinogens
1. Alkylating agents
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
2. Acylating agents
1-Acetyl-imidazole
Dimethylcarbamyl chloride

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Indirect Acting Agents

Polycyclic and heterocyclic aromatic hydrocarbons
Benz[*a*]anthracene
Benzo[*a*]pyrene
Aromatic amines, amides, azo dyes
★2-Naphthylamine (β-naphthylamine) ★**bladder cancer in workers exposed to aniline dye & rubber industry**
2-Acetylaminofluorene
Dimethylaminoazobenzene (butter yellow)
Natural plant and microbial products
★Aflatoxin B1 ★**hepatocellular carcinoma**
Griseofulvin
Betel nuts
Others
Nitrosamine and amides
★Asbestos, nickel, chromium ★ **lung cancer**
Insecticides, fungicides, Vinyl chloride, Arsenic
Polychlorinated biphenyls (PCBs)

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B) Radiation Carcinogenesis

1. UV radiation of sunlight:

- can cause skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas).
- At greatest risk are fair-skinned people
- Due to inability to repair environmentally induced DNA damage.
- E.g. Xeroderma pigmentosum

2. Ionizing radiation:

- (e.g. X-rays, nuclear bombs)

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C) Viral & Microbial Carcinogenesis

1. RNA viruses (retroviruses):

- Human T-cell leukemia virus-1 (HTLV-1):

2. DNA viruses:

- Human Papillomavirus (HPV)
- Epstein-Barr virus (EBV)
- Human Herpesvirus 8 (HHV-8)
- Hepatitis B virus (HBV)

3. Helicobacter Pylori:

- Associated with gastric carcinoma & gastric lymphoma

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Human Papilloma Virus (HPV):

- **HPV (types 1, 2, 4, 7):** cause benign squamous papillomas (warts in human)
- **HPV (types 16, 18, 31):** involved in the genesis of oropharyngeal, cervical, anal, perianal, and penile cancers

Epstein-Barr Virus:

- Involved in the pathogenesis of several human tumors:
  - Burkitt lymphoma
  - AIDS-related lymphomas
  - Nasopharyngeal carcinoma

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Hepatitis B Virus:

- associated with **hepatocellular carcinoma**
- HCV is also linked to hepatocellular carcinoma

Helicobacter Pylori

- gram negative spiral bacteria
- associated with 90% of duodenal ulcers, and 70-90% of gastric ulcers
- the likely cause for gastric carcinoma & lymphoma (MALToma: marginal zone associated lymphoma)

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Four classes of genes are targets of genetic damage

1. The growth promoting **proto-oncogenes**
2. The growth-inhibiting **tumor-suppressor genes** (anti-oncogenes)
3. Genes that regulate apoptosis
4. The DNA repair genes

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Six fundamental changes in cell physiology that together dictate malignant phenotype

1. Self-sufficiency in growth signals **(oncogenes)**
2. Insensitivity to growth-inhibitory signals **(Cancer Suppressor Genes)**
3. Evasion of apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Ability to invade and metastasize

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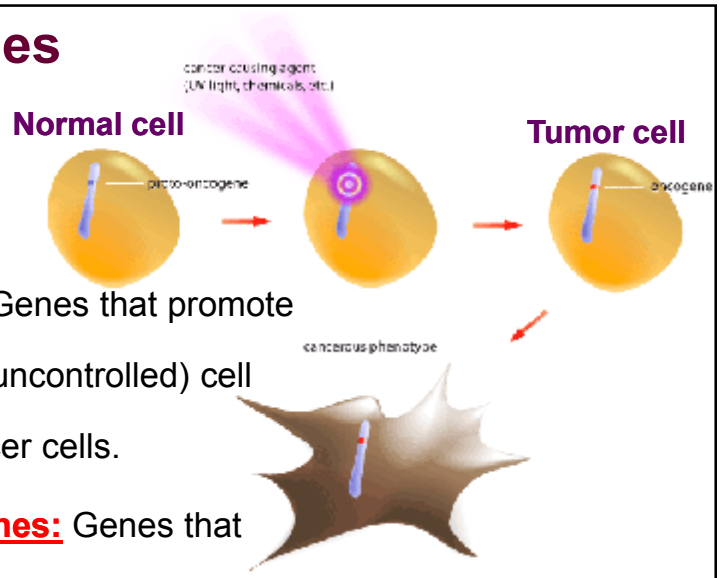
Oncogenes



Oncogenes: Genes that promote autonomous (uncontrolled) cell growth in cancer cells.

Protooncogenes: Genes that promote normal growth and differentiation

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Oncogenes

- They are derived by mutations in proto-oncogenes
- characterized by the ability to promote cell growth in the absence of normal growth-promoting signals.
- Their products, called ***oncoproteins***, resemble the normal products of proto-oncogenes except that oncoproteins are devoid of important regulatory elements
- Encode oncoproteins as growth factors, receptors, signal transducers, transcription factors, and cell-cycle components
- **History**: Varmus & Bishop first recognized their presence within the genome of transforming retroviruses (**v-onc**)

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Self-Sufficiency in Growth Signals

Growth Factors:

- All normal cells require stimulation by growth factors to undergo proliferation.
- Many cancer cells acquire growth self-sufficiency, however, by acquiring the ability to synthesize the same growth factors to which they are responsive.

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Self-Sufficiency in Growth Signals

Growth Factor Receptors:

- Mutations and pathologic overexpression of normal forms of growth factor receptors have been detected in several tumors.
- e.g. the epidermal growth factor (EGF) receptor is overexpressed in 80% of squamous cell carcinomas of the lung.

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Cancer Suppressor Genes

- Both normal alleles of the Rb gene must be inactivated (two hits) for the development of retinoblastoma

Knudson (two hit theory):

- In hereditary retinoblastoma, children are born with one normal and one defective copy of the Rb gene (**first hit**).
- They lose the normal copy by some somatic mutation (**second hit**).

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Tumor Suppressor Genes: p53

- located on chromosome 17
- It's the most common **Tumor Suppressor Gene** target for genetic alterations in human tumors
- More than 50% of human tumors contain mutations in this gene
- Familial loss causes **Li-Fraumeni syndrome** (multiple tumors) includes sarcomas, breast cancer, leukemia, brain tumors, and carcinomas of the adrenal cortex

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Tumor Angiogenesis

- **Angiogenesis is required for:**
  1. continued tumor growth
  2. metastasis
- Tumors can not enlarge beyond 1-2 mm in diameter or thickness unless they are vascularized
- The 1-2 mm zone represents the maximal distance across which oxygen and nutrients can diffuse from blood vessels. Beyond this distance the tumor fails to enlarge without vascularization. Hypoxia will induce apoptosis by activation of p53

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How Do Growing Tumor Develop a Blood Supply

- Tumor growth is controlled by the balance between angiogenic factors, & antiangiogenesis molecules.
- **Examples of angiogenic factors:**
  - Vascular endothelial growth factor (VEGF)
  - Basic fibroblast growth factor (bFGF)
- **Examples of antiangiogenesis are:**
  - thrombospondin-1, angiostatin, endostatin, & vasculostatin.

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Angiogenesis

- Hypoxia within the growing tumor favors angiogenesis by release of hypoxia-inducibale factor–1 (HIF-1).
- HIF-1 controls transcription of VEGF
- Transcription of VEGF is under the control of Ras oncogene
- **Ras oncogene** activation upregulates the production of VEGF
- Proteases are involved in regulating the balance between angiogenic and antiangiogenic factors

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Angiogenesis

- P53 inhibits angiogenesis by inducing the synthesis of the antiangiogenic molecule thrombospondin-1
- With mutational inactivation of both p53 alleles, the level of thrombospondin-1 drop markedly tilting the balance in favor of angiogenic factors
- Some success in the treatment of cancer has been achieved through the use of angiogenesis inhibitors such as endostatin

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Mechanism of Invasion & Metastasis

- **Metastatic process can be divided into two phases:**
  1. **Invasion of the extracellular matrix**
  2. **Vascular dissemination and homing of tumor cells**
- E-cadherin acts as intercellular glue that bind cells together.
- E-cadherin function is lost in almost all epithelial cancer

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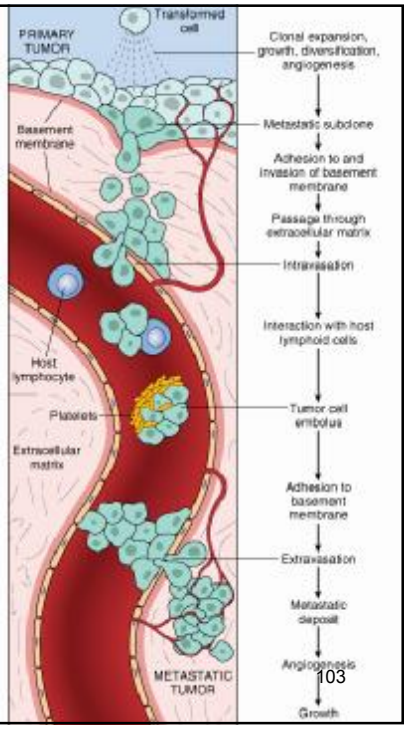
Sequential steps involved in the hematogenous spread of a tumor



- **Invasion of the cellular matrix in 4 steps:**
  1. Detachment of tumor cells from each other
  2. Attachment of tumor cells to matrix components
  3. Degradation of ECM
  4. Migration of tumor cells

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Invasion of the extracellular matrix

- Attachment of tumor cells to ECM proteins such as laminin and fibronectin
- Local degradation of the basement membrane and interstitial connective tissue
  - Tumor cells either secrete proteolytic enzymes themselves or induce the host cells fibroblasts to elaborate proteases
  - Several of metalloproteinases including gelatinases, collagenases, and stromelysins, cathepsin-D are involved
  - Benign tumors show little **type IV collagenase** activity, whereas their malignant counterpart overexpresses this enzyme

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Summary

- **Neoplasia-** an abnormal mass of tissue which has lost its responsiveness to growth controls

Benign neoplasms:

- slow-growing
- well-differentiated tumors
- lack the ability to metastasize
- remain localized
- amenable to surgery

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Summary

Malignant neoplasms

- fast-growing lesions
- invade normal structures
- vary in the degree of differentiation
- some show anaplasia
- capable of metastasis

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