MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437

Pathology

teamwork 437

Lecture: Neoplasia

Color Index :-

- **VERY IMPORTANT**
- **Extra explanation**
- **Examples**
- **Diseases names: Underlined**
- **Definitions**

*{فإن تحيى فما قيمة العلم إن كان سهلا ميسرا}

OBJECTIVES:

- Definitions: neoplasm, tumor, oncology.
- Classification of tumors into benign and malignant.
- Nomenclature of tumors.
- Characteristics of benign and malignant tumors.
- Definitions: teratoma, hamartoma, choristoma.
- To understand that the incidence of cancer varies with age, race, geographic and genetic factors.
- To explain the genetic predisposition to cancer.
- To identify the precancerous conditions.
- To list the various causes of tumors.
- Compare between benign & malignant tumors in terms of differentiation, rate of growth, local invasion, & metastases.
- Identify the morphological features that differentiate between benign & malignant tumors.
- Define the terms: differentiation & anaplasia.
- List the pathways by which malignant tumors spread (and how).
- Define the terms: dysplasia & carcinoma in situ.
- To define the host defenses against cancer
- To define tumor grade & clinical stage.
- To define cachexia & its causes.
- To define a paraneoplastic syndrome & know examples of tumors associated with endocrinopathies, osseous, vascular and hematologic changes.

OBJECTIVES:

- To be familiar with the general principles, value, procedures, and applications of biopsies, exfoliative & aspiration cytology and frozen sections.

- To list examples of tests used to diagnose cancer: immunohistochemistry & flow cytometry.

- To discuss the use of molecular diagnostic testing in the setting of cancer diagnosis & prognosis.
- Role of genetic damage and the resultant mutation in the neoplastic proliferation (clonal expansion) process.

- What are the targets of genetic damage?

- Main changes in the cell physiology that lead to formation of the malignant phenotype:
  a) Self-sufficiency in growth signals.
  b) Insensitivity to growth inhibitory signals.
  c) Evasion of apoptosis.
  d) Limitless replicative potential.
  e) Sustained angiogenesis.
  f) Ability to invade and metastasize.

- Definition and tole of “oncogenes” and “tumor suppressor genes” with examples (e.G. P53, her-2, ras,...etc.)

- Role of DNA repair genes

- Understanding of “tumor

- Progression” concept.

- Important karyotypic changes in tumors.

INTRODUCTION TO NEOPLASM (OVERVIEW)

- **What is cancer ?** Cancer is the second cause of death in the United States (For those who are curious, heart diseases, namely strokes, top the list). It causes emotional and physical suffering to the patient. It has different mortality rates.
  - -Some are curable such as Hodgkin lymphoma
  - Others are fatal such as pancreatic adenocarcinoma

Neoplasia: (new growth) is an abnormal mass of tissue. It is the growth of which is uncoordinated with that of normal tissues, which still persist in the same excessive manner even after the cessation (توقف) of the stimulus which evoked (أحدث) the change.

Some terms than you need to know :-

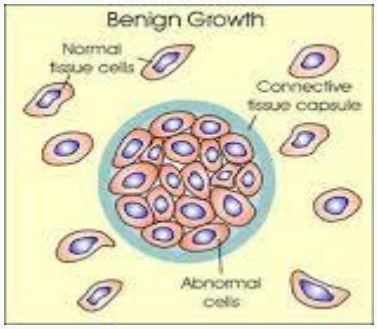
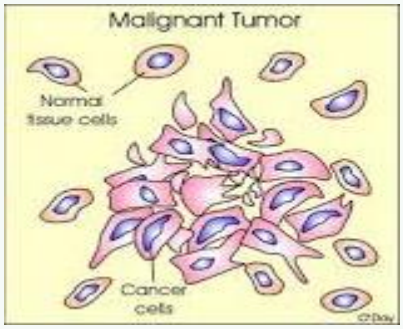
- **Neoplasm** = often is referred to as a tumor. (Neoplasia: literally means "new growth").
- **Tumor** (ورم)= swelling (in the clinical settings, tumor is usually used interchangeably with neoplasia)

1. Tumors could be **malignant** (خبيث) = cancers.
2. Or could be **Benign = (حميد)**

- **Oncology** = The study of tumors . (Oncos = tumor) + (ology = study of)

In the beginning we should understand that normally, in every cell, there are molecular "accelerators" بنزينand "breaks"فرامل .The neoplastic cells have gain the function of the accelerators, and loss the function of the breaks. Imagine you have this car with a stuck accelerator, and the brakes are not working... This crazy car resembles a cancer cells ☹

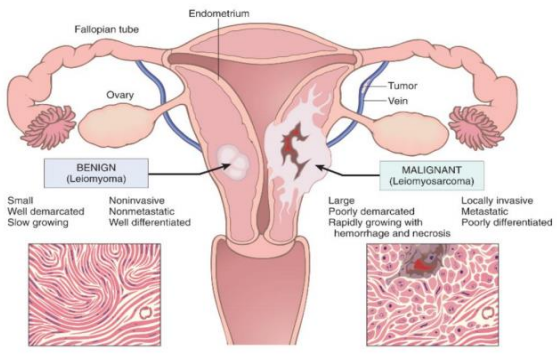
DEFINITIONS

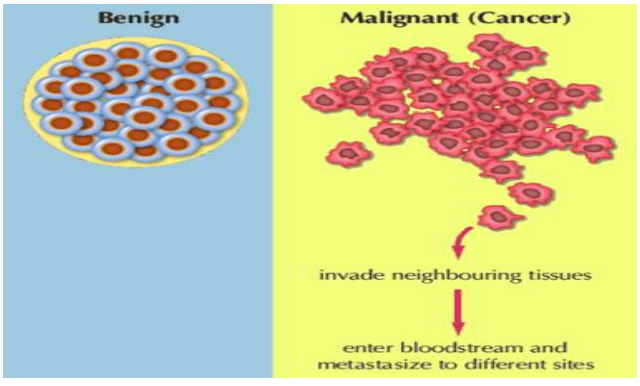
Benign (حميد):	Malignant (خبيث):
• Microscopic and gross characteristics of the lesion "ضرر" are considered to be relatively **innocent** "simple" . • Tumors remain **localized**. • Tumors are **amenable** "قابل" to **local surgical removal**. • Patients generally (usually) **survive**. • Well circumscribed =bounded or confined "مقيدة\محصورة"	Microscopic and gross characteristics of the lesion can **invade**"يجتاح\ينتهك" and **destroy adjacent structures** and **spread** "ينتشر" **to distant sites (metastasize)** to **cause death**. *There is a different between : Invade: mean locally Invade (Invade invasion) direct في مكان معين بالقلب مثلاً Spread: spread to distant sites (metastasize) يعني كان بالرجل وصار بالرأس مثلاً
	

Note that :

-The division of neoplasms into benign and malignant categories is **based on their potential clinical behavior. And parenchymal component**.

- Benign tumors generally can be locally excised (removed).





CLASSIFICATION OF TUMORS

All tumors, benign and malignant, **have two basic component**

The parenchyma : made up of transformed or neoplastic cells.

stroma : The supporting, host-derived, non-neoplastic made up of connective tissue, blood vessels, and host-derived inflammatory cells.

The parenchyma:
- Determines the biological behavior of the tumor.
- From which the tumor derives its name.

The stroma:
- Carries the blood supply.
- Provides support for the growth of the parenchyma.

- So The **nomenclature of tumors and their biologic behavior** are based primarily on the parenchymal component
- However, **the growth and evolution of tumors** is critically dependent on their stroma as an adequate stromal blood supply is a requisite for the tumor cells to live and divide.

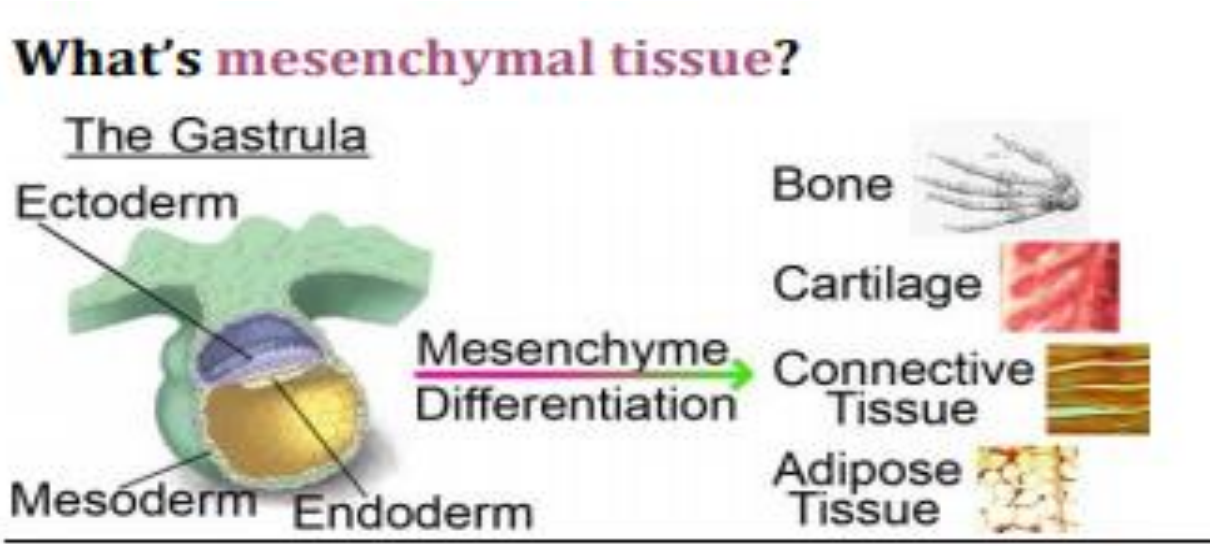
NOTES :

-Why we call them transformed? Because they lose control and go crazy and they evade all regularity mechanisms

- Supporting stroma is host derived it means that it is from the victim (the host), it consists of: C.T. around the tumor, including(fibroblasts, blood vessels and inflammatory cells.) The tumor needs it because it needs the blood vessels to grow, live and proliferate.

Additional Slide: we advise you to go through it before studying the next slides

- **Benign**
  - Arise from:
    - Epithelial: (glands | lining organs)
      - Appearance +Type of organ
        - Cyst (أكياس)
        - Polyp (نتوءات)
        - Papilloma (granule)
        - Adenoma
    - Mesenchymal *use the suffix (oma)
      - Bone
      - Cartilage
      - Adipose tissue
      - Connective tissue
- **Malignant**
  - Arise from:
    - Epithelial (poorly differentiate) *use the suffix (carcinoma)
      - Glandular pattern (Adenocarcinoma)
      - Produce squamous cell (squamous cell carcinoma)
    - Mesenchymal *use the suffix (sarcoma)
      - Bone
      - Cartilage
      - Adipose tissue
      - Connective tissue



NOMENCLATURE OF TUMORS - BENIGN

- Benign tumors are designated by attaching the suffix **- *oma*** to the cell type from which the tumor arises.

- The nomenclature of mesenchymal tumors usually apply this rule e.g. :-

  - Benign tumor arising in fibrous tissue: Fibro + oma = Fibroma
  - Benign tumor arising in cartilage: chondro + oma = chondroma .
  - Benign tumor arising in bone tissue. : Oste + oma = Osteoma
  - Benign tumor arising in fatty tissue: Lipo + oma = lipoma
  - Benign tumor arising in striated(skeletal) muscle: Rhabdomyo + oma = rhabdomyoma
  - Benign tumor arising in smooth muscle: Leiomyo + oma = leiomyoma

The nomenclature of benign epithelial tumors is more complex: **cell of origin, microscopic pattern or macroscopic appearance**.

Adenoma is generally applied to benign epithelial neoplasms producing gland patterns and to neoplasms derived from glands but not necessarily exhibiting glandular patterns.

Examples of benign epithelial neoplasms:

- ➢ - Respiratory airways: Bronchial adenoma.
- ➢ - Renal epithelium: Renal tubular adenoma.
- ➢ - Liver cell: Liver cell adenoma.
- ➢ - Squamous epithelium: squamous papilloma.

Some glaring inconsistencies may be noted. For example, the terms *lymphoma, mesothelioma, melanoma,* and *seminoma* are used for malignant neoplasms.

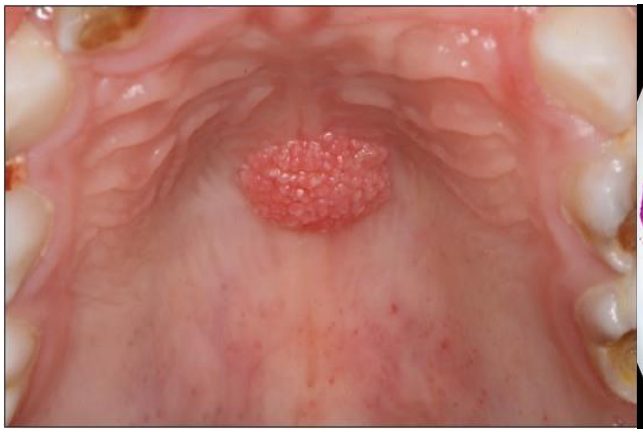
- Dysgerminoma = Malignant tumor in the ovary.

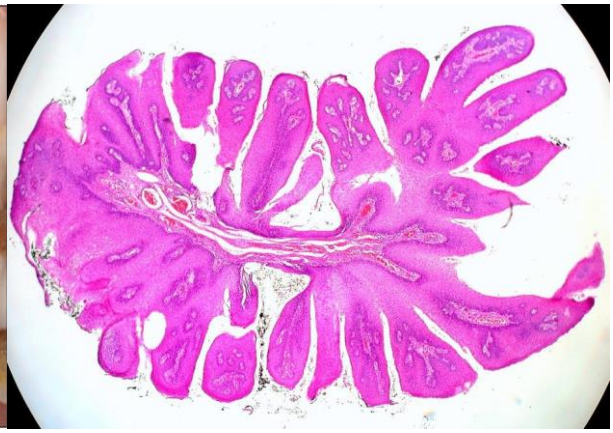
*Even though these tumors have the suffix –*oma*, they are **malignant** tumors.

*It's very important to memorize the exceptions above.

NOMENCLATURE OF TUMORS - BENIGN

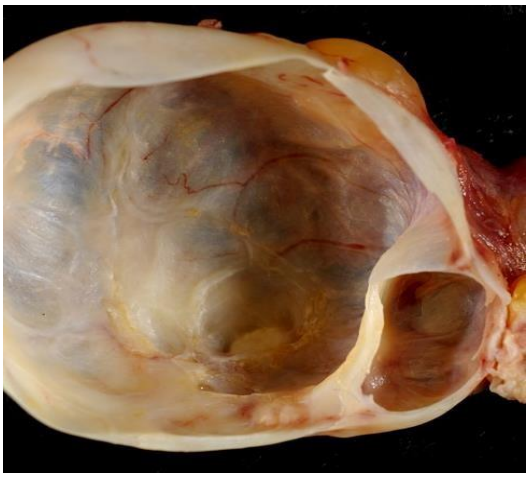
- Benign epithelial neoplasms producing microscopically or macroscopically visible finger-like or warty projections from epithelial surfaces are referred to as **papillomas**.



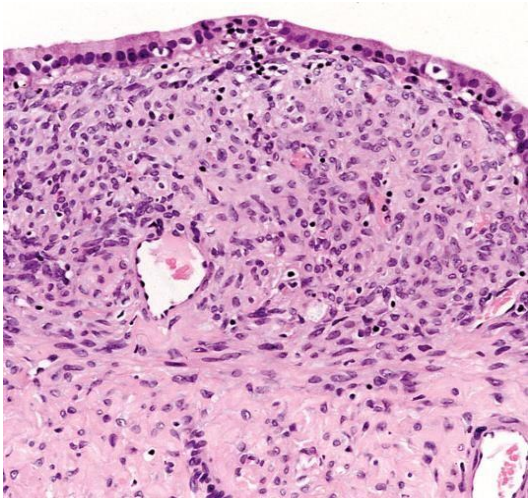


- Benign epithelial neoplasms forming large cystic masses, as in the ovary, are referred to as **cystadenomas**.

Macroscopically (GROSS)



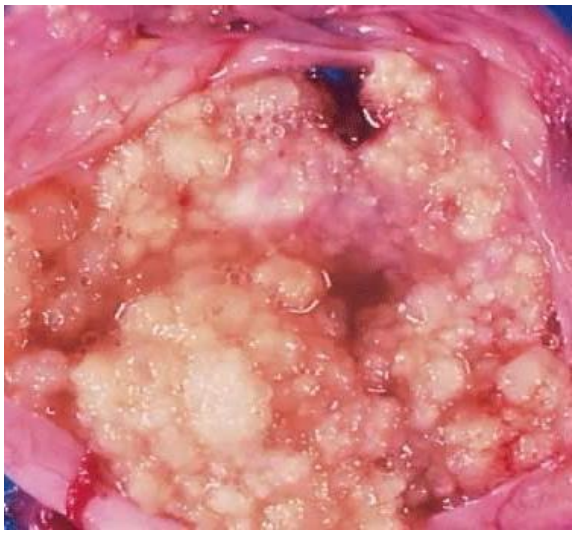
Microscopically



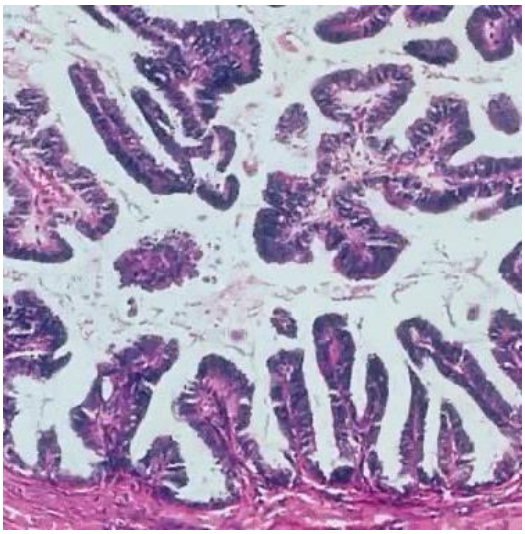
NOMENCLATURE OF TUMORS - BENIGN

- Some of the latter produce papillary patterns that protrude into cystic spaces and are called ***pupillary cystadenomas***

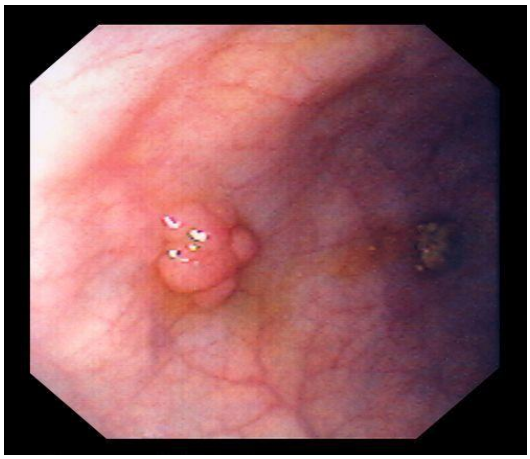
Macroscopically

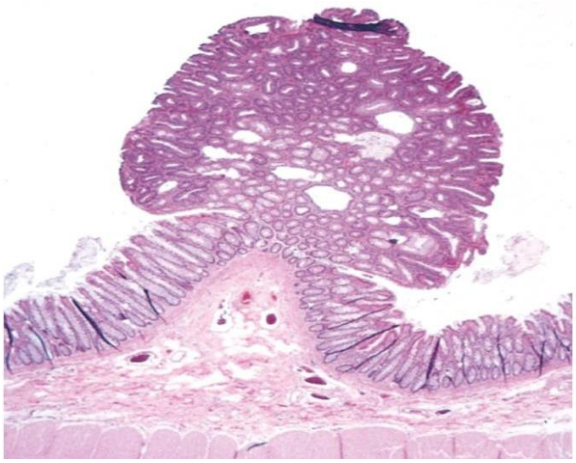


Microscopically

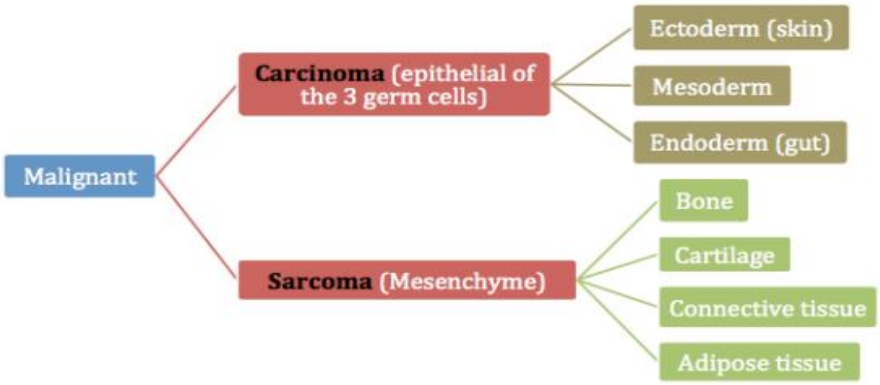


- ***Polyp :*** is a mass that projects above a mucosal surface, as in the gut, to form a macroscopically visible structure

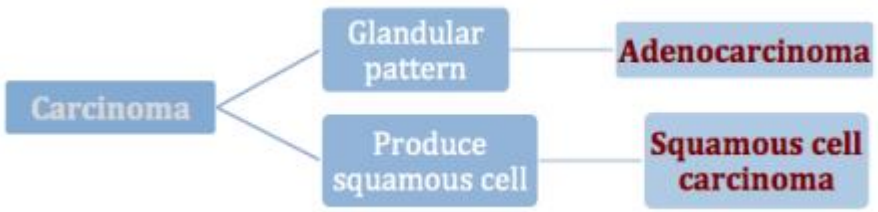




NOMENCLATURE OF TUMORS - MALIGNANT

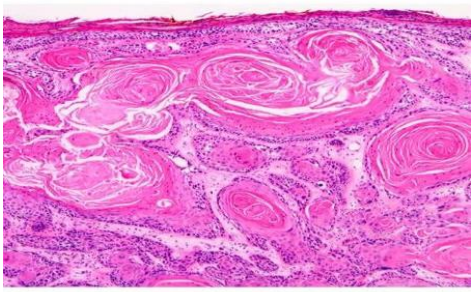


- Malignant neoplasms arising in **mesenchymal tissues** are called *sarcomas*.
  - Fibrosarcoma: a malignant tumor arising in fibrous tissue.
  - Chondrosarcoma: a malignant tumor arising in cartilaginous tissue.
  - Osteosarcoma: a malignant tumor arising in bone tissue.

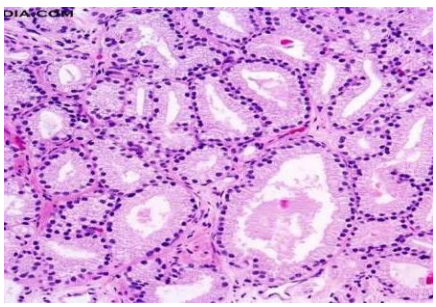


- Malignant neoplasms arising from **epithelial cells** are called *carcinomas*.
- Carcinomas include:
  - Carcinomas that arise from glandular epithelial cells (with or without forming glands): *adenocarcinomas*
  - Carcinomas that arise from squamous cells (some producing keratin): *squamous cell carcinomas.*
  - Carcinomas that show little or no differentiation: *poorly differentiated or undifferentiated carcinoma.*

Squamous cell carcinoma



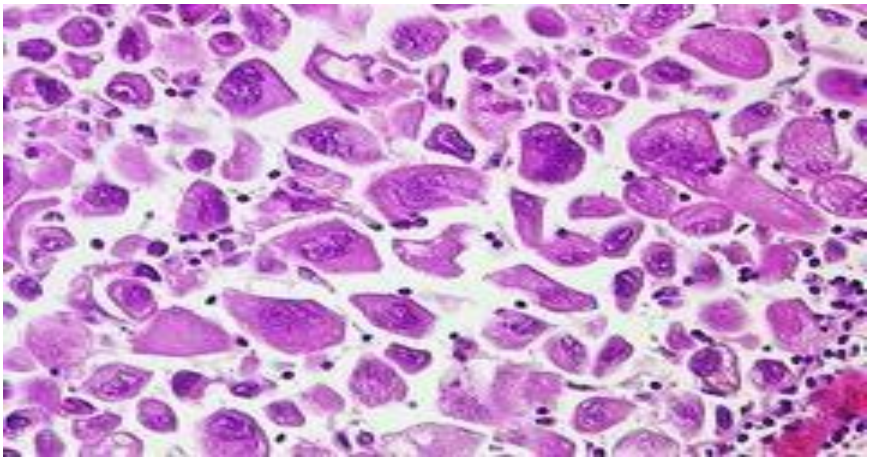
Adenocarcinoma



cells that have the keratin (which is the out most layer of the skin pearls keratin malignant Squamous cell carcinoma انها نعرف بالاختبار تجي فلما MALIGNANT

In the other hand adenocacarcinoma forming tubules (prostatic)

- Not infrequently, however, a cancer is composed of undifferentiated cells of unknown tissue origin, and must be designated merely as an ***undifferentiated malignant tumor.***



- The transformed cells in a neoplasm, whether benign or malignant, often resemble each other, as though all had been derived from a single progenitor, consistent with the
- monoclonal origin of tumors.(Most tumors arise from a single cell = monoclonal = almost they are samillar)

- In some unusual instances, however, *divergent differentiation* of a single neoplastic clone along two lineages occurs, creating the so-called *mixed tumors*. (In some tumors Has the ability to differentiate into epithelial cell / mesenchymal half of generations epithelial cell and other mesenchymal)

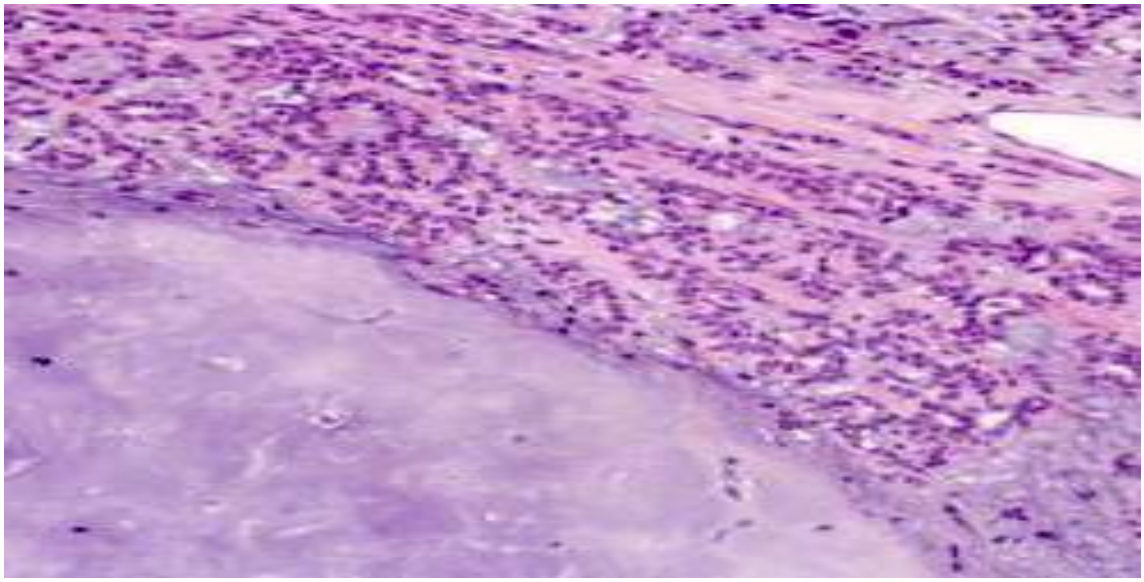
- The best example is the mixed tumor of the salivary gland. These tumors have obvious epithelial components dispersed throughout a fibromyxoid stroma, sometimes harboring islands of cartilage or bone.
- All of these diverse elements are thought to derive from a single clone capable of giving rise to epithelial cells or myoepithelial cells, or both, and the preferred designation for these neoplasms is **pleomorphic adenoma.**

Pleomorphic= متعددة شكلا

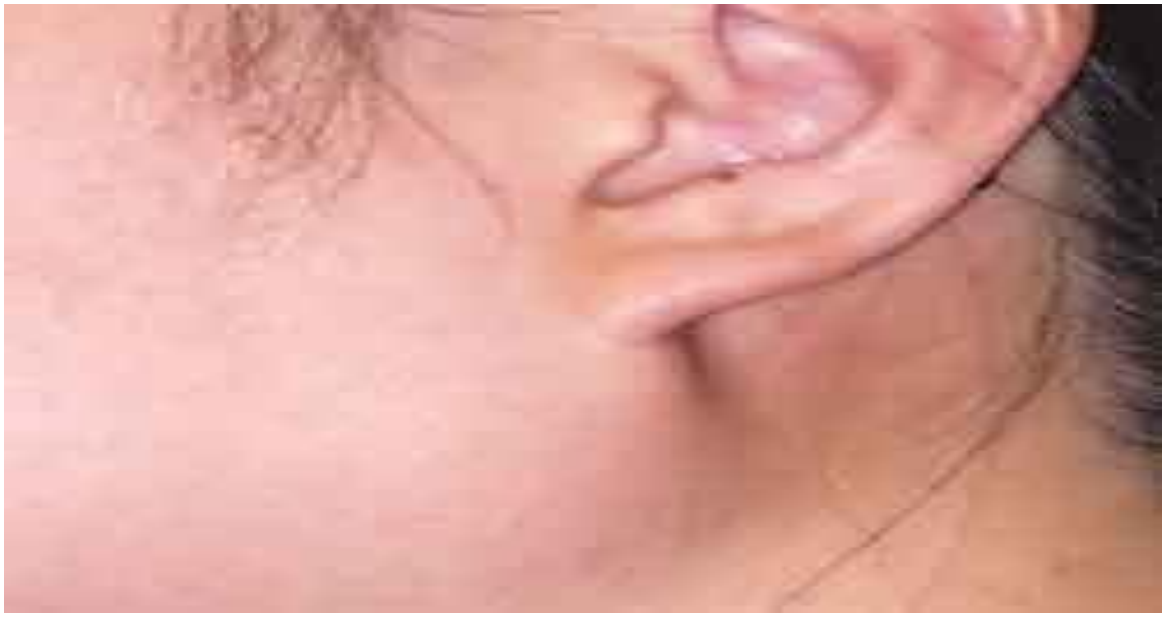
It is benign tumor rising from gland.

PLEOMORPHIC ADENOMA

Microscopically



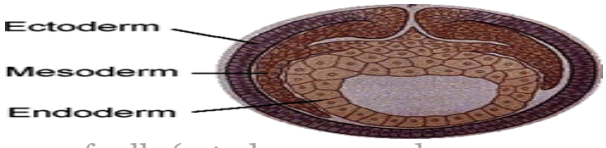
Macroscopically



TERATOMA :

They have high ability to differentiate into almost every kind of tissue in the body. it gives different type of cell in one cell. 90% are found in the germ cells while 10% found in the sequestered midline embryonic rests

- It is a special type of **mixed tumor** that contains recognizable **mature** or **immature** cells or tissues representative of more than one germ cell layer and sometimes all three.



- But what is Germ cell?: consist from three layers of cells (ectoderm, mesoderm, and endoderm) that are formed in the early embryo.
  " مجموعة الخلايا التي تنتج من عملية التكوين الجنيني، ومنها تتكون الأعضاء
  هناك ٣ طبقات كل منها سيكون مسؤول عن إنتاج أعضاء معينة"

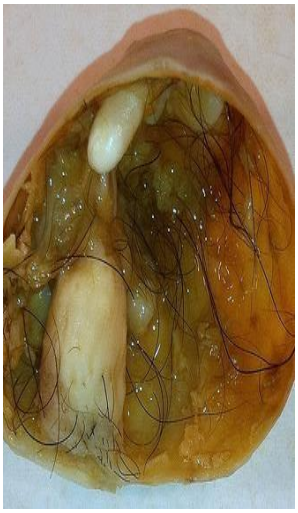
- Teratoma originates from totipotential cells (an embryonic cell that is capable of developing into any variety of body cells) such as those normally present in the ovary and testis and sometimes abnormally present in sequestered *midline embryonic rests*. Such cells have the capacity to differentiate into any cell type found in the adult body (they may give rise to neoplasms that mimic bone, epithelium, muscle, fat, nerve and other tissues).

- Most common sites are the **ovary** and **testis**.

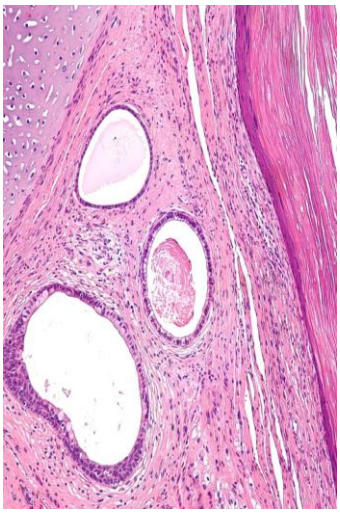
- When all the components within the teratoma are well differentiated:
  Benign → (mature) teratoma.

- When all the components within the teratoma are less differentiated (potentially or overtly) :
  Malignant → (immature) teratoma.

Macroscopic (gross):



Microscopic:

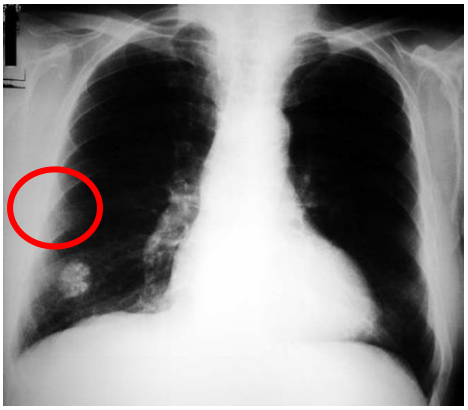


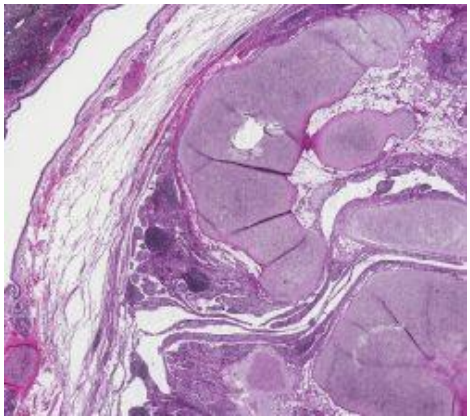
HAMARTOMA :

It grows at the same rate as the surrounding tissues. It is composed of tissue elements normally found at that site, but which are growing in a disorganized mass.

- is a **mass of disorganized** benign-looking tissue indigenous to the particular site.
- For example, *pulmonary chondroid hamartoma,* contains **islands of disorganized**, but **histologically normal cartilage, bronchi, and vessels**.
- Hamartomas have traditionally been considered developmental malformations "abnormally formed part of the body", but some genetic studies have shown the presence of acquired translocations, suggesting a neoplastic origin.

Pulmonary Hamartoma





CHORISTOMA :

organized structure ، لكن بالمكان الغلط يكون:
Another name :Ectopic tissue

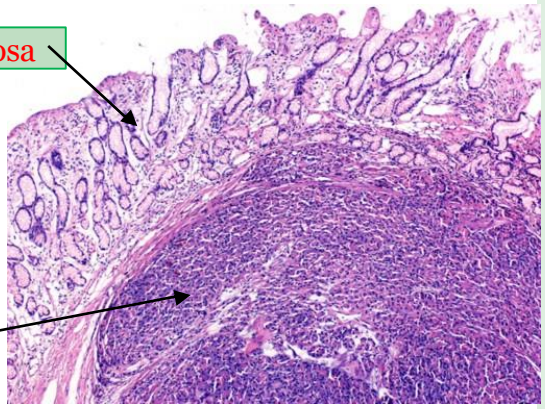
- is a congenital anomaly consisting of a heterotopic rest of cells.

  Heterotopia : is the presence of a particular tissue type at a non-physiological site,

- For example, a small nodule of well-developed and normally organized pancreatic tissue may be found in the submucosa of the stomach, duodenum, or small intestine.
- It has **usual trivial significance.**
- is normal tissue growth in an abnormal location

Gastric mucosa

Pancreatic tissue

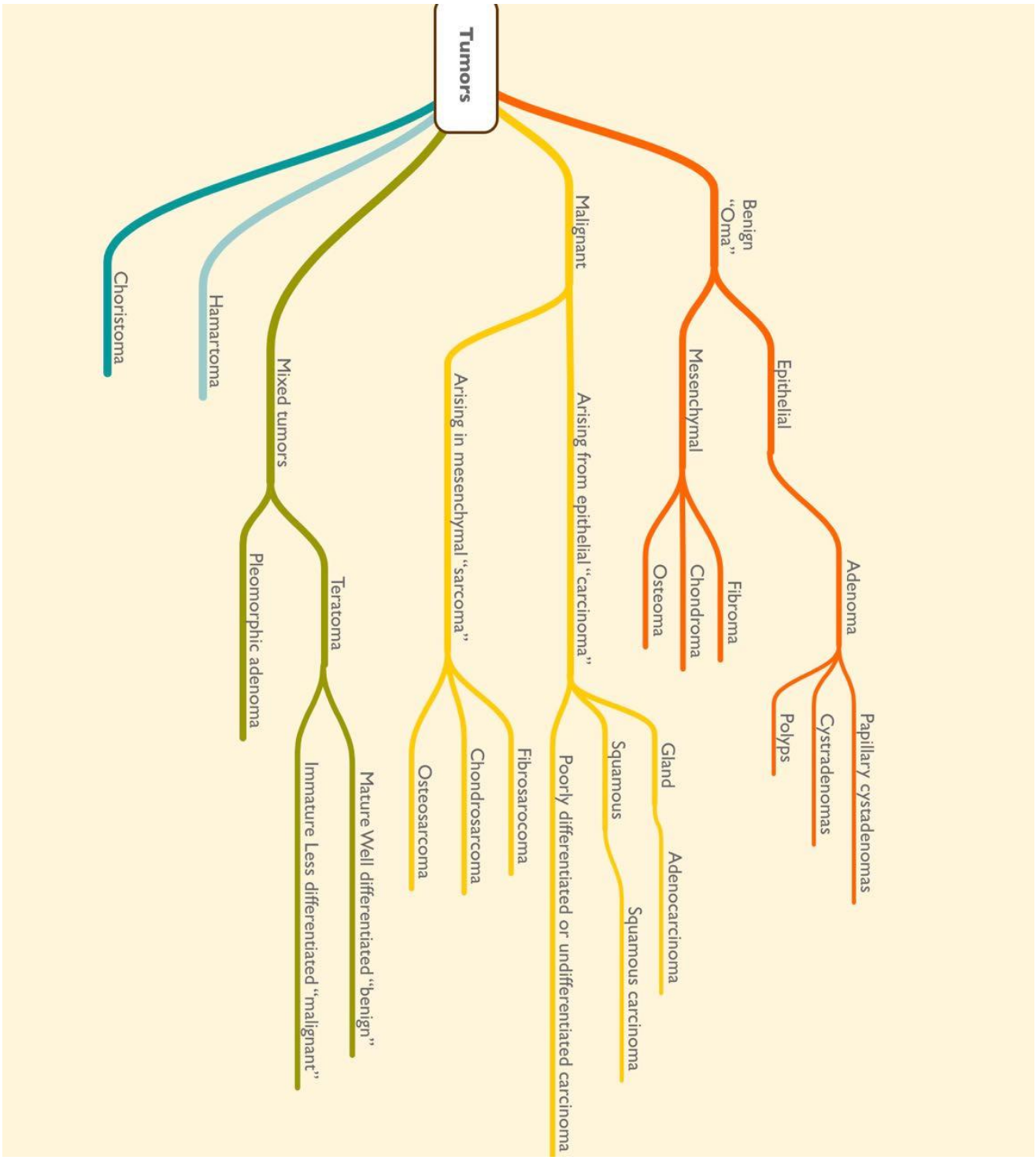


SUMMARY :

- Although the terminology of neoplasms is regrettably not simple, a firm grasp of the nomenclature is important because it is the language by which the nature and significance of tumors are categorized.

Tissue of Origin	Benign	Malignant
Composed of One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
Endothelial and related tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Tumors of epithelial origin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Urothelial papilloma	Urothelial carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma
More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived from One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)	Malignant mixed tumor of salivary gland
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived from More Than One Germ Cell Layer—Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

SUMMARY



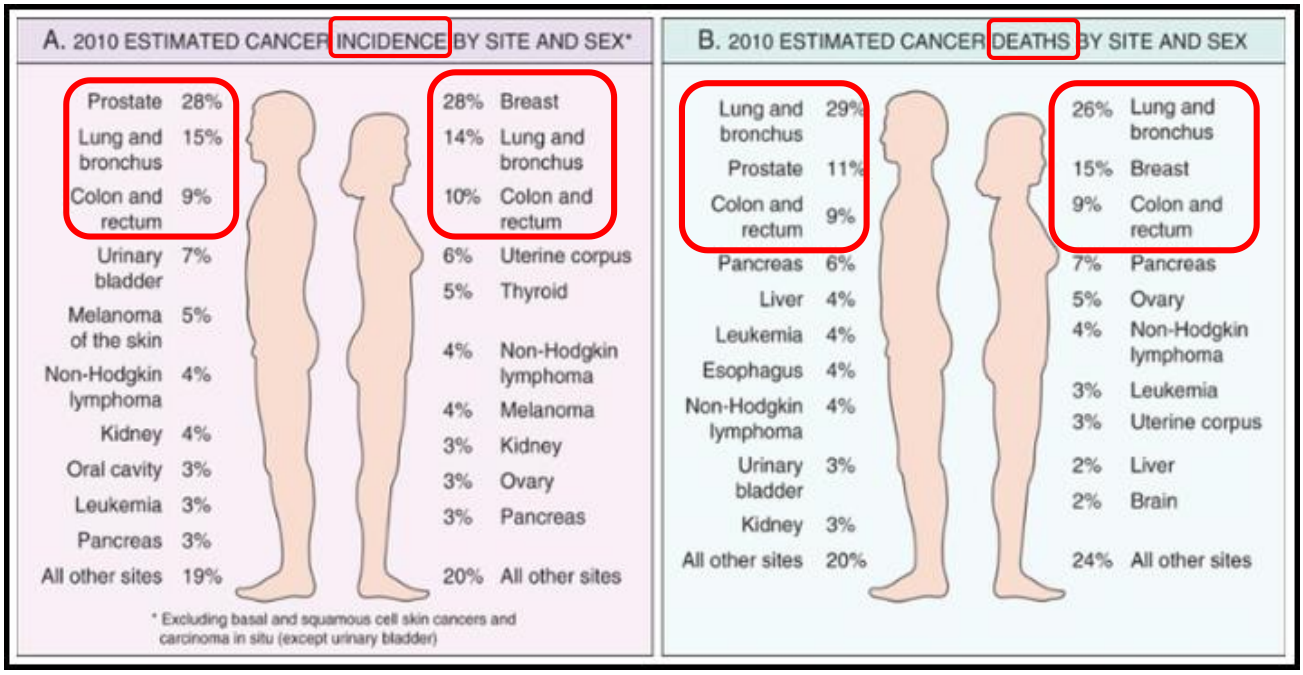
MSQ's (TEST YOURSELF!)
Room name: PATH437
click here

Epidemiology of tumors

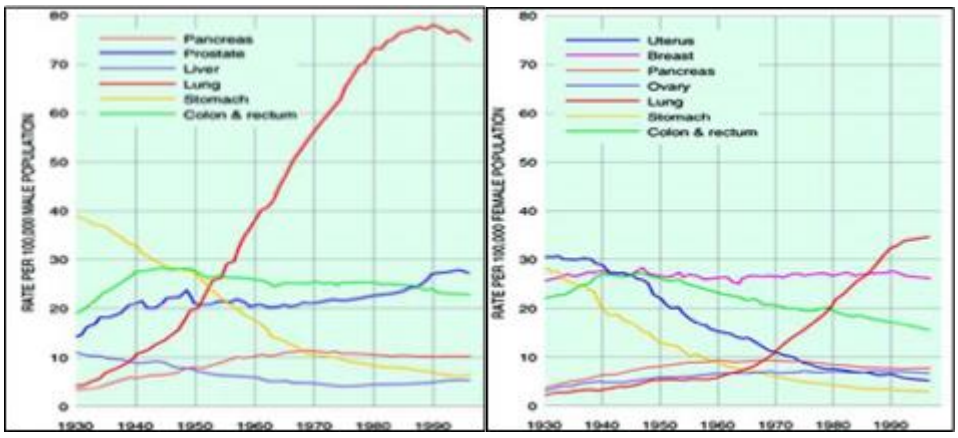
Studying the **epidemiology** of tumors will aid in the following:

- Discover etiologic factors
- Plan preventive measures
- Know what types of tumors are common and what are rare
- Develop screening methods for early diagnosis

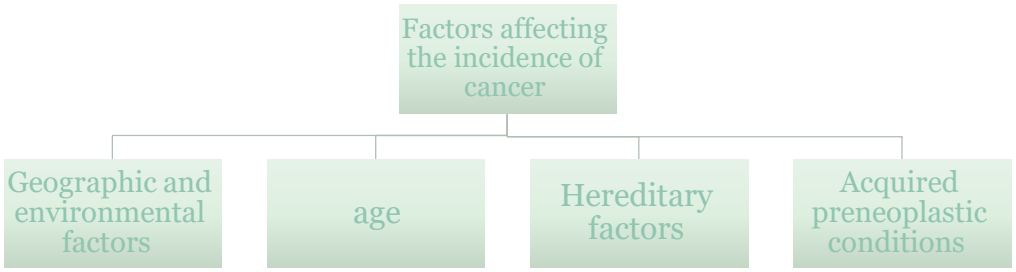
Cancer Incidence



- the most common **killer** in **both sexes** is the **lung cancer**
- memorize the percentages inside the red square.



Notice the increase of lung cancer in females in the last 40 years. On the other hand, lung cancer in males started decreasing in the last 30 years.



1) Geographic & Environmental Factors :

- The rate of gastric carcinoma in **Japan** is 7 times its rate in North America & Europe.
- The rate of breast carcinoma in **North America** is 5 times its rate in Japan.
- Liver cell carcinoma is more common in **African** populations.

- Exposure to asbestos => **mesothelioma**
- Smoking => **lung carcinoma**
- Multiple sexual partners => **cervical carcinoma**
- Fat-rich diet => **colon carcinoma**

2) Age:

- Generally, the frequency of cancer **increases with age**.

- Most cancer mortality occurs between **55 and 75** years of age and it also **increases during childhood**

- The most common malignant tumors **in children** are:

- Leukemia
- CNS tumors
- Lymphomas
- Soft tissue & bone sarcomas.

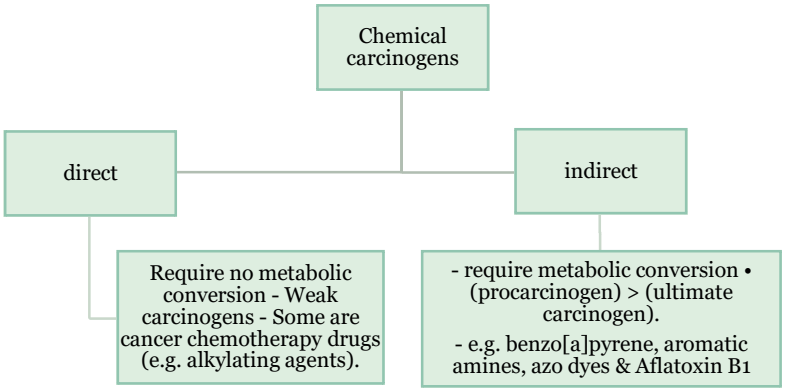
Agent/Group of Agents	Human Cancer Site and Type for Which Reasonable Evidence Is Available	Typical Use/Occurrence
Arsenic and arsenic compounds	Lung, skin, hemangiosarcoma	Byproduct of metal smelting Component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, mesothelioma; gastrointestinal tract (esophagus, stomach, large intestine)	Formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire-resistant textiles, friction materials (e.g., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Leukemia	Principal component of light oil Many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents Formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung	Missile fuel and space vehicles Hardener for lightweight compounds metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate	Uses include yellow pigments and phosphors Found in solders Used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung	Component of metal alloys, paints, pigments, and preservatives
Ethylene oxide	Leukemia	Ripening agent for fruits and nuts Used in rocket propellant and chemical synthesis, in fumigants for foodstuffs and textiles, and in sterilants for hospital equipment
Nickel compounds	Nose, lung	Nickel plating Component of ferrous alloys, ceramics, and batteries Byproduct of stainless steel arc welding
Radon and its decay products	Lung	From decay of minerals containing uranium Can be serious hazard in quarries and mines
Vinyl chloride	Angiosarcoma, liver	Refrigerant Monomer for vinyl polymers Adhesive for plastics Formerly used as inert aerosol propellant in pressurized containers

ACQUIRED PRE-NEOPLASTIC DISORDERS

Some Clinical conditions that predispose to cancer:

- Dysplastic bronchial mucosa in smokers → lung carcinoma
- Liver cirrhosis → liver cell carcinoma
- Margins of chronic skin fistula → Squamous cell carcinoma
- Endometrial hyperplasia → endometrial carcinoma
- Leukoplakia of the oral cavity, vulva or penis → squamous cell carcinoma
- Villous adenoma of the colon or rectum → colorectal adenocarcinoma

ETIOLOGY OF TUMORS



1- Chemical Carcinogens

- Chemical carcinogens can be natural or synthetic. (the only thing they have in common is that they lead to cancer)
- They can cause cellular damage via:

1. **Direct**

   -They require no metabolic conversion to become carcinogenic.

   -They are in general weak carcinogens but are important because some of them are cancer chemotherapy drugs (e.g. alkylating agents).

2. **Indirect** (They're not carcinogenic but when they come to the body, the body makes enzymatic changes that will lead to cancerous metabolites)

   - They require metabolic conversion of the chemical (*procarcinogen*) to active &
   - carcinogenic products (*ultimate ncarcinogen).*
   - e.g. benzo[a]pyrene, aromatic amines, azo dyes & Aflatoxin B

• **Mechanisms of action:**

- Most chemical carcinogens are mutagenic i.e. cause genetic mutations.
  - ❖the commonly mutated oncogenes & tumor suppressors are **RAS** and **TP53**.
- All direct chemical carcinogens & ultimate chemical carcinogens are highly reactive as they have electron-deficient atoms.
- They react with the electron rich atoms in the **RNA, DNA & other cellular proteins**.

Chemical Carcinogens

❑**Alkylating agents :**

- Polycyclic hydrocarbons
  - Cigarette smoking
  - Animal fats during broiling meats. (some of the meats' hydrocarbon will be converted to aromatic hydrocarbon)
  - Smoked meats & fish . (have aromatic and cyclo hydrocarbon like benezeprene)

- - (Directly active) Some of the chemotherapeutic substances (cyclophosphamide) Eg. patient with Huntington's disease will be given chemo and will be cured.. he may develop cancer after the chemotherapy.
- - Alkylating agents are like monkeys; they hold different DNA strands at the same time producing defects in DNA replication.
- - If alkylating agents are harmful, why are they used in chemotherapy to treat cancer? As we have mentioned they work on producing defects in DNA replication. Cancer cells replicate their DNA a lot. Therefore, cancer cells are at increased risk of defects in DNA replication; and we hope these defects will lead to its death.

❑**Aromatic amines & azo dyes**:

- **B-naphthylamine** cause bladder cancer in rubber industries & aniline dye.
- Some **azo dyes**, used to color food, cause bladder cancer.

it's not an active substance. When inhaled it's not active but after it has gone through the liver and stomach it goes to the urinary bladder and stays there for a while. In this stage, there's an exposure of these active carcinogenic cells to the transitional epithelium and causes cancer. But if the B-naphthylamine is put in the urinary bladder without modification it will not cause cancer because it's inactive.

Direct-Acting Carcinogens
Alkylating Agents
β-Propiolactone
Dimethyl sulfate
Diepoxybutane
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
Acylating Agents
1-Acetyl-imidazole
Dimethylcarbamyl chloride
Procarcinogens That Require Metabolic Activation
Polycyclic and Heterocyclic Aromatic Hydrocarbons
Benz(*a*)anthracene
Benzo(*a*)pyrene
Dibenz(*a*,*h*)anthracene
3-Methylcholanthrene
7, 12-Dimethylbenz(*a*)anthracene
Aromatic Amines, Amides, Azo Dyes
2-Naphthylamine (β-naphthylamine)
Benzidine
2-Acetylaminofluorene
Dimethylaminoazobenzene (butter yellow)

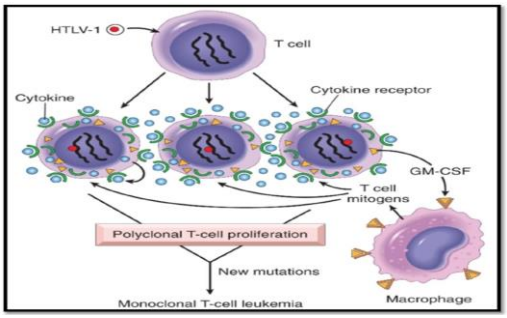
Natural Plant and Microbial Products
Aflatoxin B_1
Griseofulvin
Cycasin
Safrole
Betel nuts
Others
Nitrosamine and amides
Vinyl chloride, nickel, chromium
Insecticides, fungicides
Polychlorinated biphenyls

VIRAL & MICROBIAL ONCOGENES

Viral &microbial oncogenes include

- RNA Viruses
- DNA Viruses
- Other micro-organisms e.g.H.Pylori Bacteria

HTLV-1 Infection



- Host cells have **endogenous** gene to maintain a normal cell cycle.
- Oncogene viruses induce cellular proliferation
- **mimic or block** cellular signals necessary for the cycle regulation

*oncogene: viruses that cause tumor

RNA oncogenic viruses :

-Human T cell lymphocyte virus-1 (HTLV-1) , a retro virus , infects &transforms T-lymphocytes

-It causes **T-Cell Leukemia / Lymphoma** after a prolonged latent period (20-30 years)

-It is endemic in **Japan** &the **Caribbean**

-It is transmitted like HIV (blood & sexual relationships) but only 1% of infected patients

-develop T-cell Leukemia / Lymphoma

-No cure or vaccine to HTLV-1

-Treatment : chemotherapy with common relapses

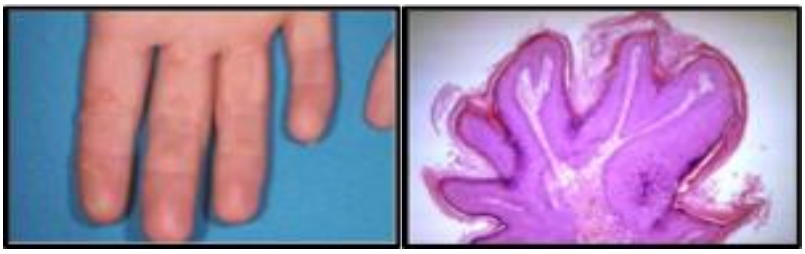
DNA oncogenic viruses : (more important than RNA)

-DNA viruses form stable associations with host DNA

-thus the transcribed viral DNA transforms the host cells (transfer to neoplastic cells)

1)Human papilloma virus (HPV),
2) Epstein Barr virus (EBV)
3)Hepatitis B virus (HBV) ,
Kaposi sarcoma herpes virus (KSHV, Called human herpesvirus-8 [HHV-8].
(HIV patients or patients with immunological Problems)

1. Human Papillomavirus (HPV)



- Has more than 70 types
- HPV types 6 and 11 cause **benign** tumors.
- **Squamous cell carcinoma** (malignant) of:
  - cervix.
  - anogenital region.
  - mouth.
  - larynx.
- It is **sexually** transmitted.
  - **Cervical cancer**: 85% have types 16 and 18 (**malignant**)
  - **Genital warts**: types 6 and 11 (**Benign**)
- HPV causing malignant tumors :
  - Types 16, 18, 31.
  - Viral DNA integrates with the host. (It loses function)
- HPV (types 16 and 18) Malignant: over-expression of Exon 6 and 7.

➢ **E6 protein binds to Rb supressor gene.**
- replaces normal transcription factors.
- decreases Rb synthesis.

(E6 protein binds to Rb tumor suppressor and releases the E2F transcription factors that normally are sequestered by Rb, promoting progression through the cell cycle)

➢ **E7 protein binds to P53.**
- facilitates degradation of P53.

- HPV infection **alone is not sufficient (enough)** to form malignancy, other risk factors must be present such as:

  - cigarette smoking.
  - coexisting infections.
  - hormonal changes.

2. Epstein-Barr Virus: (A DNA virus)

- It is a common virus worldwide.

- Infects **B lymphocytes** and **epithelial cells of oropharynx**.

Causes fever but the virus is still there in the B lymphocyte and doesn't leave for a while.

- causes infectious mononucleosis.

- EBV infection may cause malignancy:

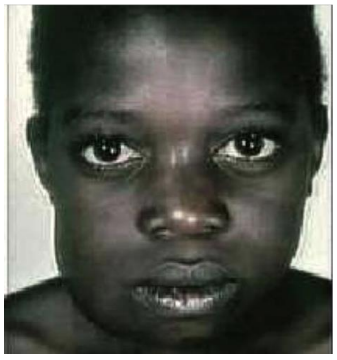
  - Burkitt's Lymphoma.
  - B cell lymphoma in immunosuppressed patients.
  - Nasopharyngeal carcinoma.

- Epstein-Barr Virus related:

➢ Nasopharyngeal carcinoma:

  - Cancer of nasopharyngeal epithelium.
  - Endemic in South China, parts of Africa.
  - **100%** of tumors contain EBV genome in **endemic areas**.

➢ BurkittLymphoma:



  - highly malignant **B cell** tumor.
  - sporadic rare occurrence worldwide.
  - most common childhood tumor in **Africa**.
  - all cases have **t(8:14)** translocation between the chromosomes 8 & 14.
  - causes **B lymphocytes proliferation**.
  - loss of growth regulation.

3. Hepatitis B virus (HBV)

- Strong association with Liver Cancer.
- World-wide, but HBV infection is most common in Far East and Africa.
- HBV infection increases the risk of hepatocellular carcinoma to 200 folds.

Helicobacter Pylori23: (Rarely leads to cancer)

- bacteria infecting the stomach.
- It causes:

- Peptic ulcers
- gastric lymphoma (Mucosal Associated Lymphoid Tumor (MALT)).
- gastric carcinoma.

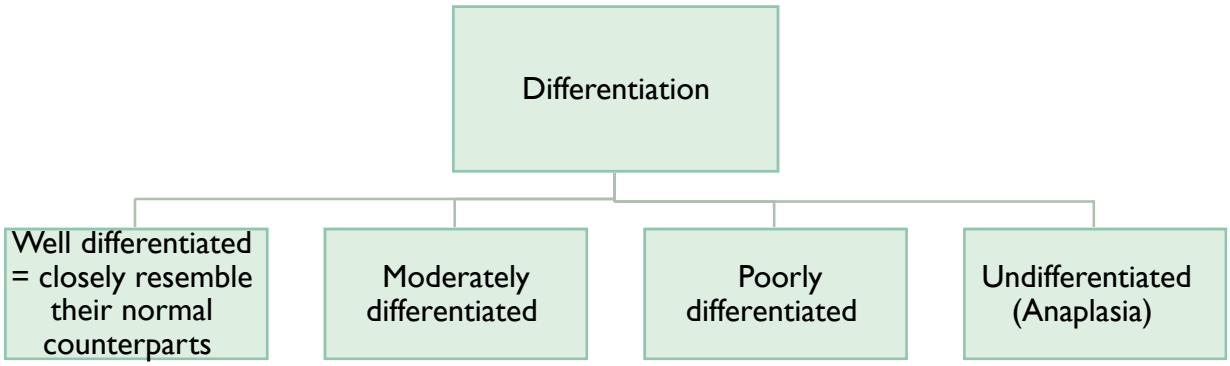
INTRODUCTION

- **Features to distinguish between benign & malignant tumors:**
  - Differentiation & Anaplasia
  - Rate of growth
  - Local invasion
  - Metastasis

- Differentiation & anaplasia are characteristics seen only in the parenchymal cells that constitute the transformed elements of neoplasms.

- **Differentiation**: the extent to which the parenchymal cells of the tumor resemble their normal counterparts morphologically and functionally.

- The more differentiated the tumor cell, the more completely it retains the functional capabilities of its normal counterparts.



COMPARISON BETWEEN BENIGN & MALIGNANT TUMORS

- **Benign Tumors:** In well-differentiated benign tumors, mitoses are usually rare and are of normal configuration.

Differentiation	Rate of growth	Local invasion	Metastases
• well-differentiated.	• They usually grow slowly. • Their growth is affected by: adequate blood supply, location, or hormones. • e.g. leiomyoma of the uterus.	• They remain localized in the site of origin. • They cannot invade. • They are usually encapsulated (*not all benign neoplasms are encapsulated).* • the lack of a capsule does not mean that a tumor is malignant.	• Do not metastasize.

COMPARISON BETWEEN BENIGN & MALIGNANT TUMORS

- **Malignant Tumors**

Metastasis (*Explained later in next slides ☺*)

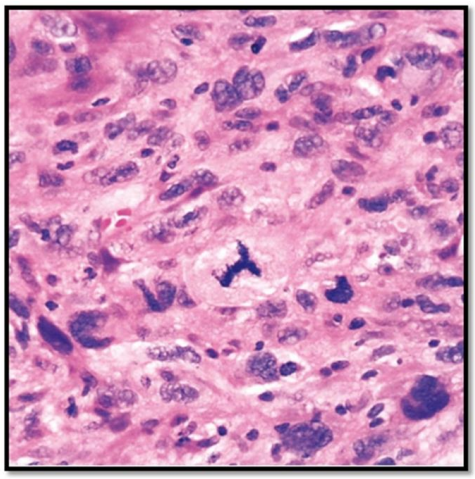
- It is the development of secondary implants of a tumor that are discontinuous with the primary tumor & located in remote tissues.
- More than any other attribute, the property of metastasis identifies a neoplasm as malignant.
- In general, the more anaplastic and the larger the primary neoplasm, the more likely is metastatic spread (but as with most rules, there are exceptions).

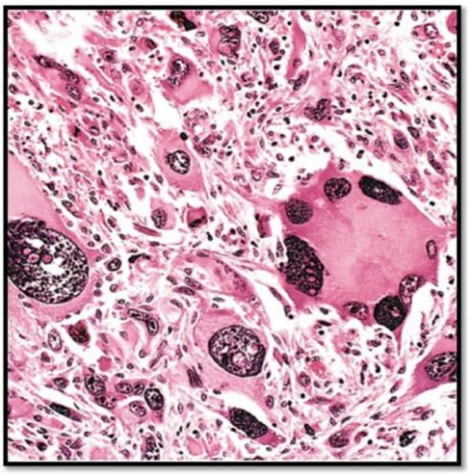
Differentiation	Rate of growth	Local invasion	Metastasis
• Malignant neoplasms are characterized by a wide range of parenchymal cell differentiation: from well differentiated to completely undifferentiated. • Between the two extremes lie tumors loosely referred to as moderately differentiated.	• They usually grow fast. • The rate of growth of malignant tumors usually correlates inversely with their level of differentiation. • The infiltrative mode of growth makes it necessary to remove a wide margin of surrounding normal tissue when surgical excision of a malignant tumor is attempted. • (عندما تتم العملية الجراحية فمن اللازم إزالة الأجزاء المحيطة بالورم عشان م انخلي فرصة ان الورم يرجع مره أخرى لان كما نعرف ان الورم الخبيث ينتشر وما يكون له نهاية محددة فلازم نشيله ونشيل الأجزاء المحيطة به)	• They invade the underlying basement membrane or stroma. • They are destructive. • They are usually not encapsulated.	• Do metastasize by one of three pathways: • (1) seeding within body cavities. • (2) lymphatic spread. • (3) hematogenous spread.

FEATURES TO DISTINGUISH BETWEEN BENIGN AND MALIGNANT TUMORS

Differentiation & anaplasia

Benign	Malignant
Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts.	Malignant neoplasms are characterized by a wide range of parenchymal cell differentiation: from well differentiated to completely undifferentiated.





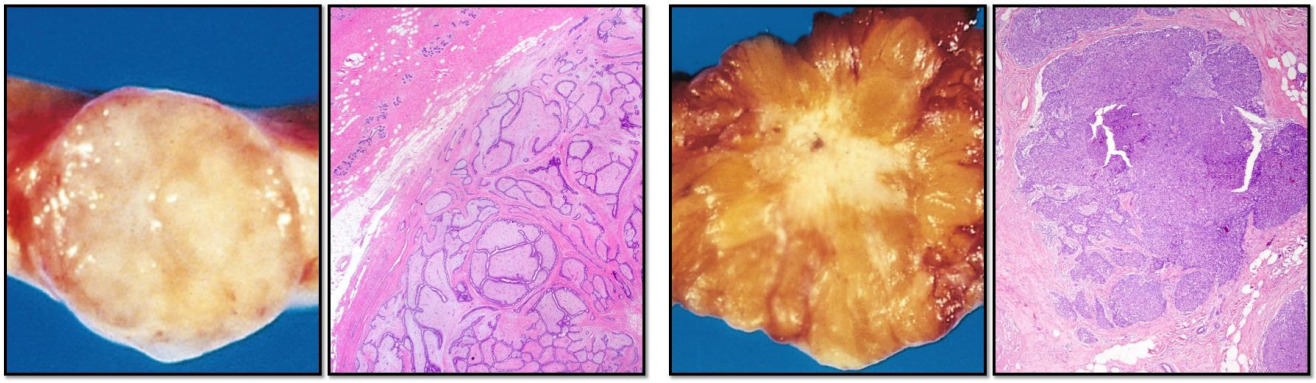
Anaplasia: loss of the structural and functional differentiation. It is a hallmark of malignancy.

Rate of growth

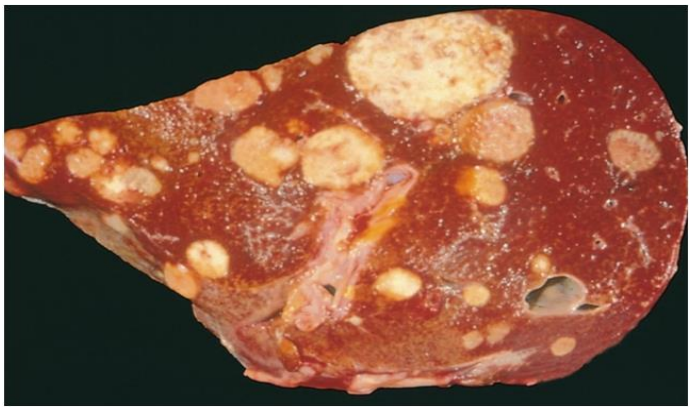
Benign	Malignant
They usually grow slowly. Their growth is affected by: adequate blood supply, location or hormones e.g. leiomyoma of the uterus.	They usually grow fast The rate of growth of malignant tumors usually correlates inversely with their level of differentiation.

Local Invasion

Benign	Malignant
They remain localized	They invade the underlying basement membrane or stroma.
They cannot invade	They are destructive.
They are *usually* encapsulated	They are *usually* not encapsulated.



Metastasis: it is the development of secondary implants of a tumor that are discontinuous with the primary tumor & located in remote tissues. More than any other attribute, the property of metastasis **identifies a neoplasm as malignant.**



Metastasis has 3 pathways:

- Lymphatic spread
- Hematogenous spread
- Seeding of the body cavities

1) Lymphatic spread:

- favored by carcinoma (Malignant epithelium).
- Breast carcinoma: metastasis to → axillary lymph nodes.
- Lung carcinomas: metastasis to → bronchial lymph nodes.

2) Hematogenous spread:

- Favored by sarcomas and are also used by carcinomas.
- Veins are commonly invaded. (because they are thinner than arteries).

Most frequently involved secondary sites:
- The two L's : lungs and liver.
- The two B's : bone and breast.

The liver is the usual location because all malignancies in the GIT can be metastasized through the portal vein.

3) Seeding of the body cavities:

- Pleural.
- Peritoneal cavities.
- Cerebral ventricles.

DIFFERENTIATION AND ANAPLASIA

Differentiation & anaplasia are characteristics seen only in the parenchymal cells that constitute the transformed elements of neoplasms.

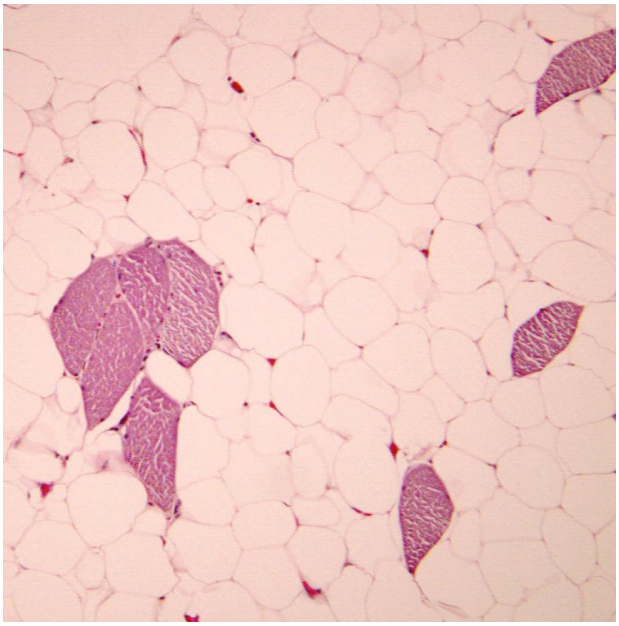
•**Differentiation:** the extent to which the parenchymal cells of the tumor resemble their normal counterparts morphologically and functionally .

Differentiation:

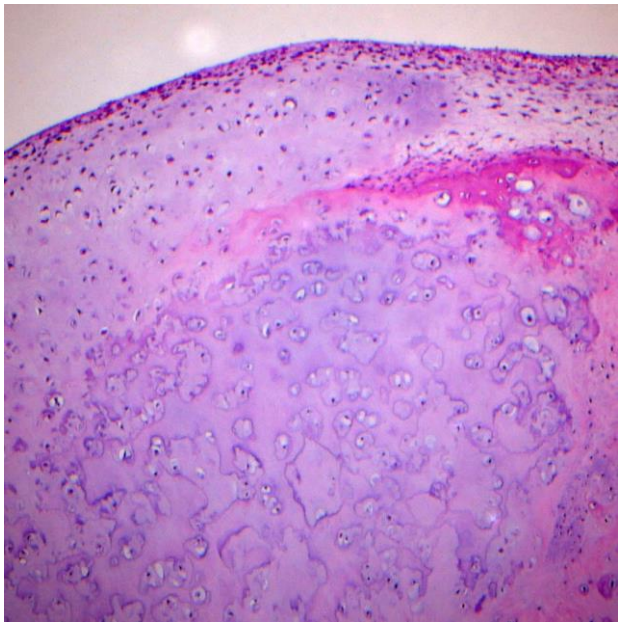
•**Well differentiated** = closely resemble their normal counterparts.
•**Moderately differentiated**
•**Poorly differentiated**
•**Undifferentiated (*Anaplasia*)**

Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts.

- **Lipoma**: mature fat cells laden with cytoplasmic lipid vacuoles.
- **Chondroma**: mature cartilage cells that synthesize their usual cartilaginous matrix (evidence of morphologic and functional differentiation).



Lipoma



Chondroma

•In **well-differentiated** benign tumors, **mitoses** are usually **rare** and are of **normal** configuration.

•The **more differentiated** the tumor cell, **the more completely** it retains the functional capabilities of its normal counterparts.

•e.g. benign neoplasms and even well-differentiated cancers of endocrine glands frequently elaborate the hormones characteristic of their origin.

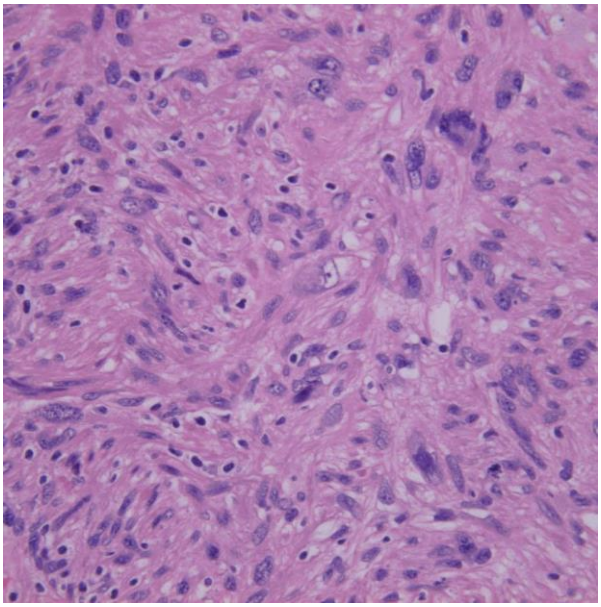
•The **stroma** carrying the blood supply is crucial to the growth of tumors **but does not aid in the separation of benign from malignant ones.**

•However the **amount of stromal connective tissue determines** the **consistency** of a neoplasm.

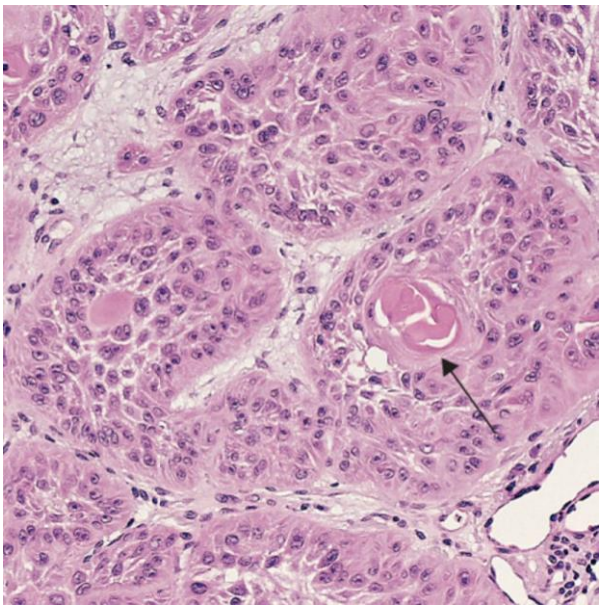
•e.g. certain cancers induce a dense, abundant fibrous stroma (*desmoplasia*), making them hard, so-called ***scirrhous*** tumors.

•**Malignant neoplasms** are characterized by a wide range of **parenchymal** cell

- differentiation: from well differentiated to completely undifferentiated.
- Between the two extremes lie tumors loosely referred to as moderately differentiated.



Leiomyosarcoma



Squamous cell carcinoma

•Malignant neoplasms that are composed of undifferentiated cells are said to be ***anaplastic.***

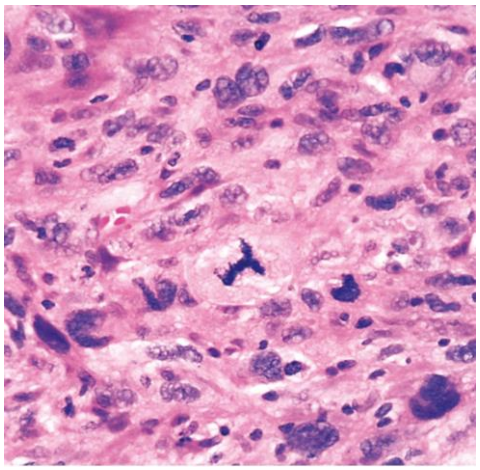
- **Anaplasia:** loss of the structural and functional differentiation. It is a hallmark of malignancy.

•It is important to recognize the following histopathological features in any neoplasm:

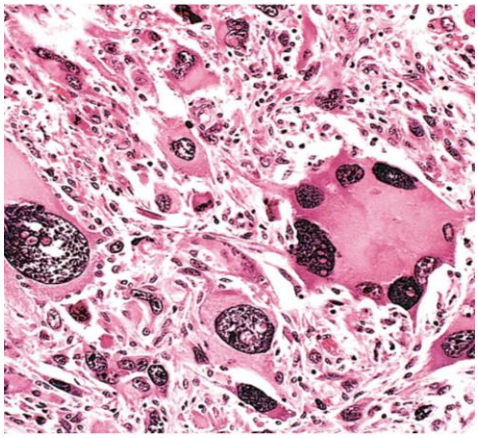
- **Pleomorphism**: variation in size and shape.
  •Enlarged nuclei: resulting in an increase of nuclear to cytoplasm ratio (that may approach 1:1 instead of the normal 1:4 or 1:6).

- **Hyperchromasia**: (dark nuclei) due to coarse & clumped chromatin.
  •Prominent nucleoli
  •Mitoses (typical or atypical forms)

- **Giant cells**: larger than their neighbors & possess either one enormous nucleus or several nuclei.



Atypical Mitosis



Tumor Giant Cells

DYSPLASIA

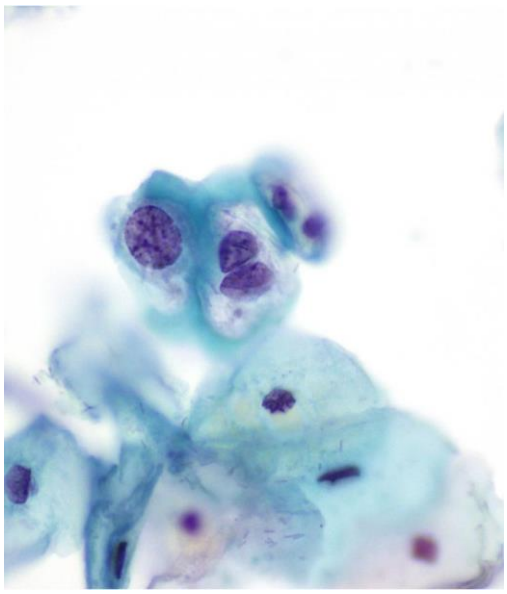
- Definition: a loss in the uniformity of the individual cells and a loss in their architectural orientation.
- It is a non-neoplastic process but a premalignant condition.

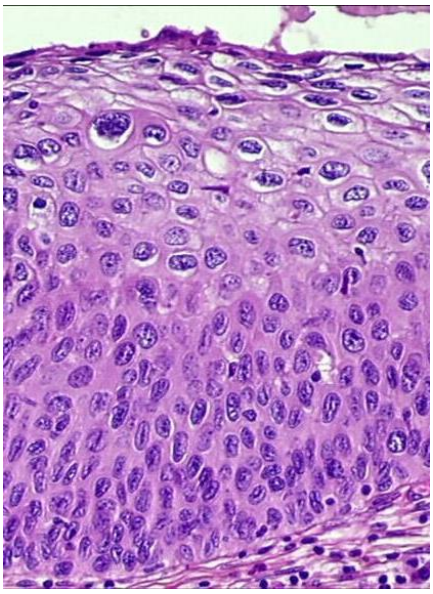
(هذا النوع هو عملية غير ورمية و لكنه شرط مسبق لحصول ورم خبيث ، يعني ما يصير الورم الخبيث الا بالمرور بهذه الخطوة)

- It occurs mainly in the epithelia.
- Dysplastic cells show a degree of: pleomorphism*, N:C ratio, Hyperchromasia**, irregular nuclei, increased mitoses, loss of polarity, & a disordered maturation or total failure of maturation.

- Dysplasia does not mean cancer.
- Dysplasia does not necessarily progress to cancer.
- Dysplasia may be reversible.
- The risk of invasive cancer varies with:
  - Grade of dysplasia (mild, moderate, severe).
  - Duration of dysplasia.
  - Site of dysplasia.

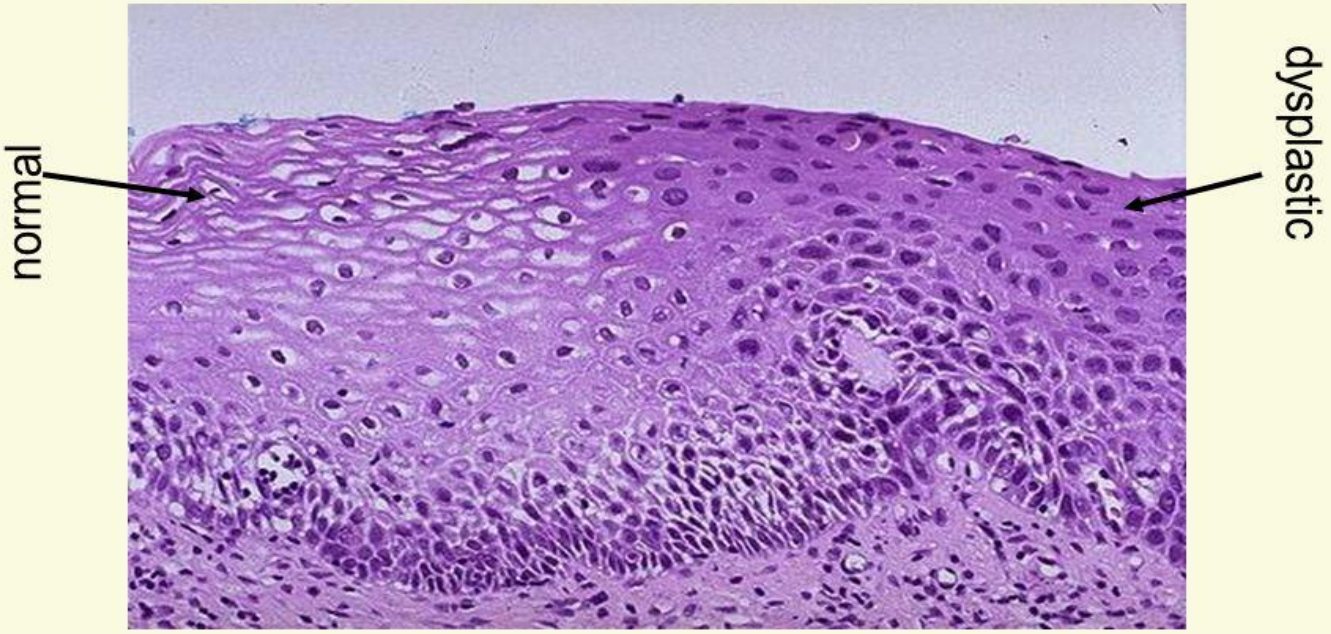
- Differences between dysplasia & cancer:
  - Lack of invasiveness.
  - Reversibility.





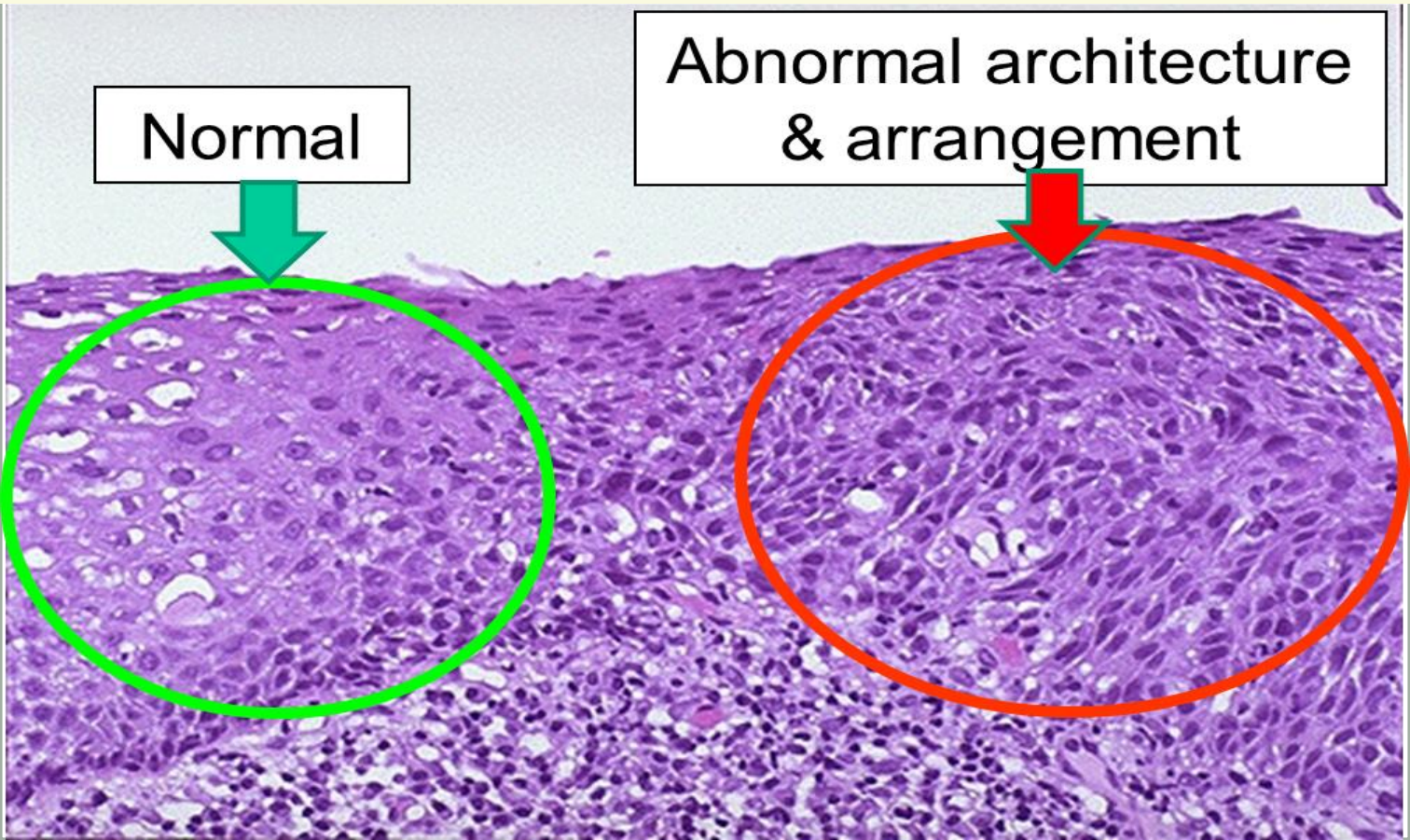
*Pleomorphism : تعدد الاشكال ** Hyperchromasia : فرط الانصباغ

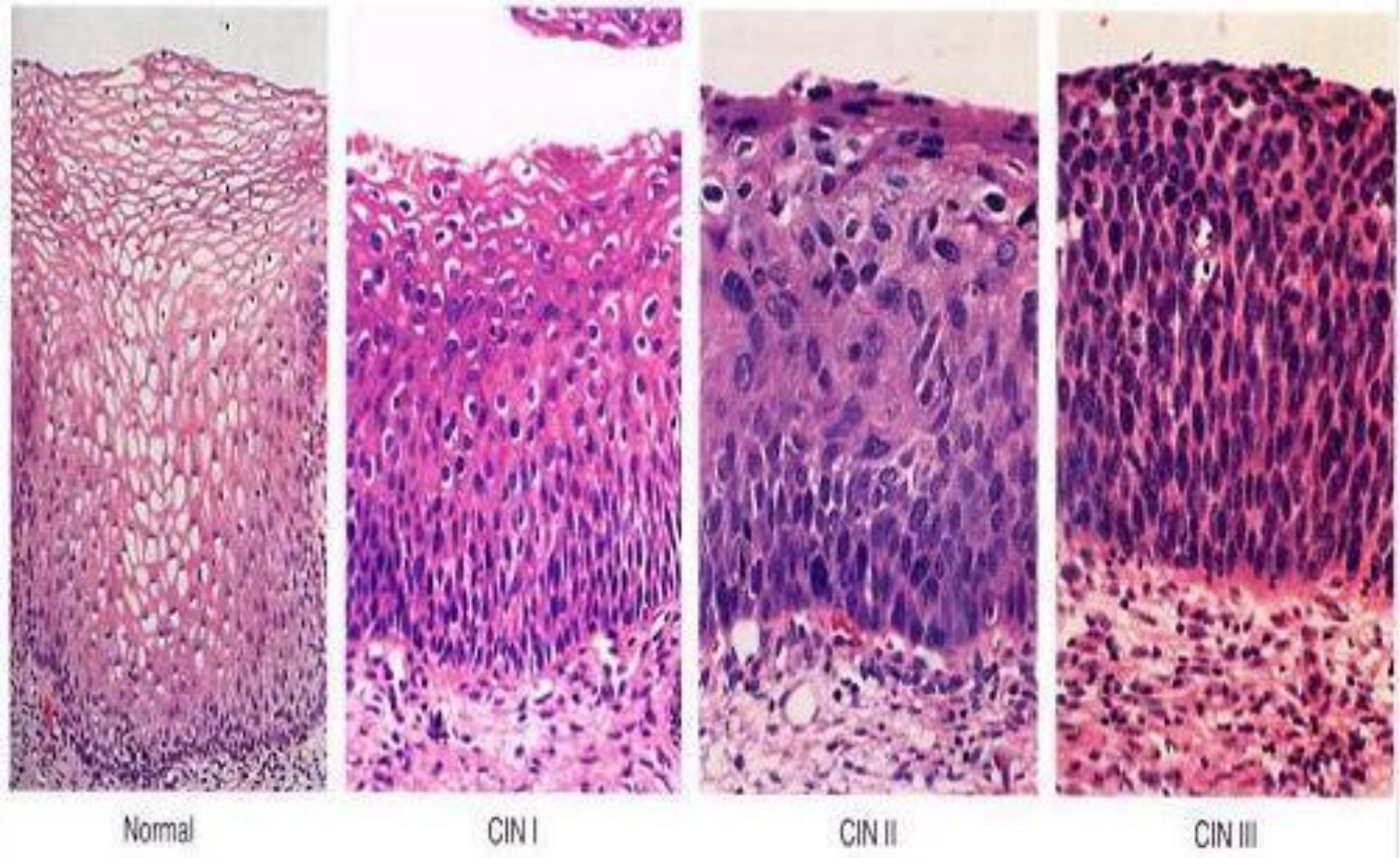
Cervical dysplasia (2)

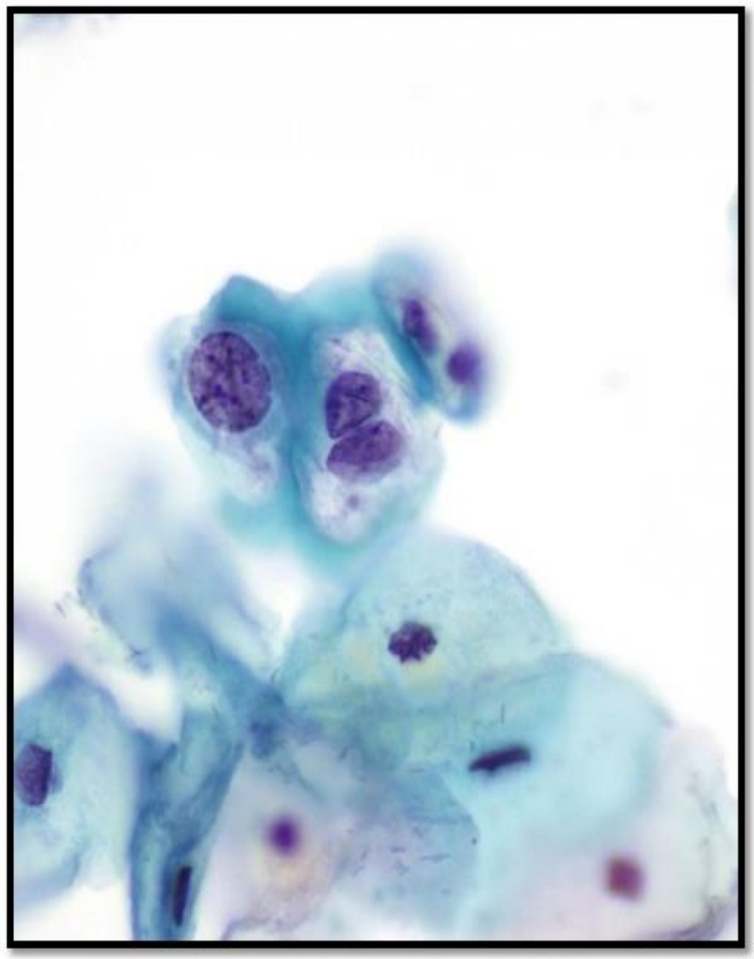


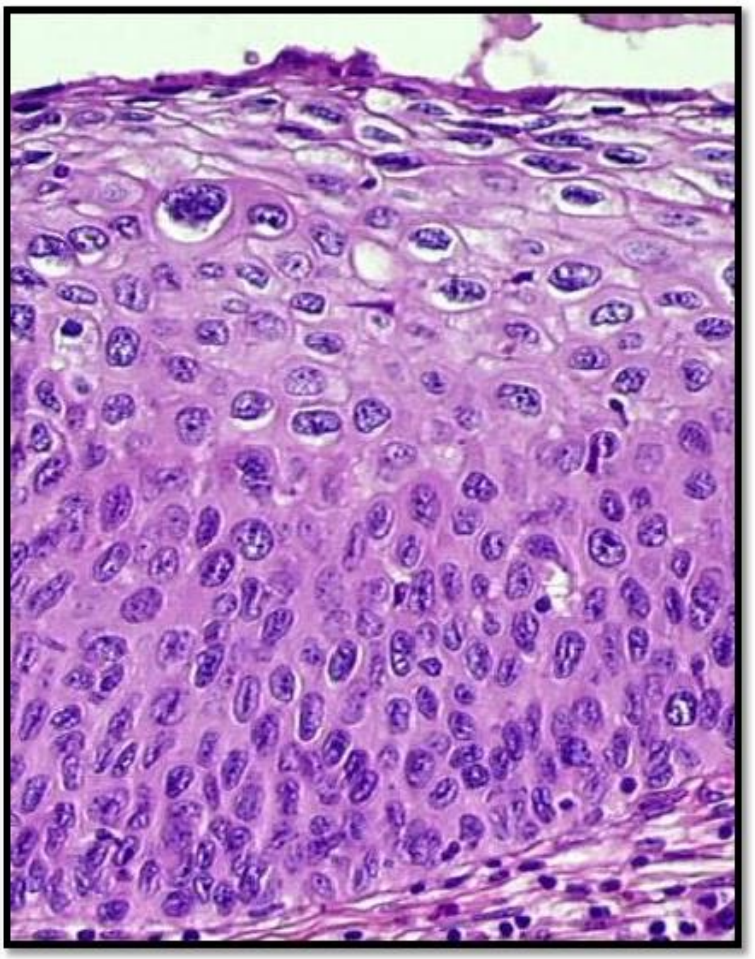
http://medlib.med.utah.edu/WebPath

- **normal** / **dysplastic** border in cervical squamous epithelium - cells become more **disorderly**




Normal
CIN I
CIN II
CIN III





CARCINOMA IN SITU

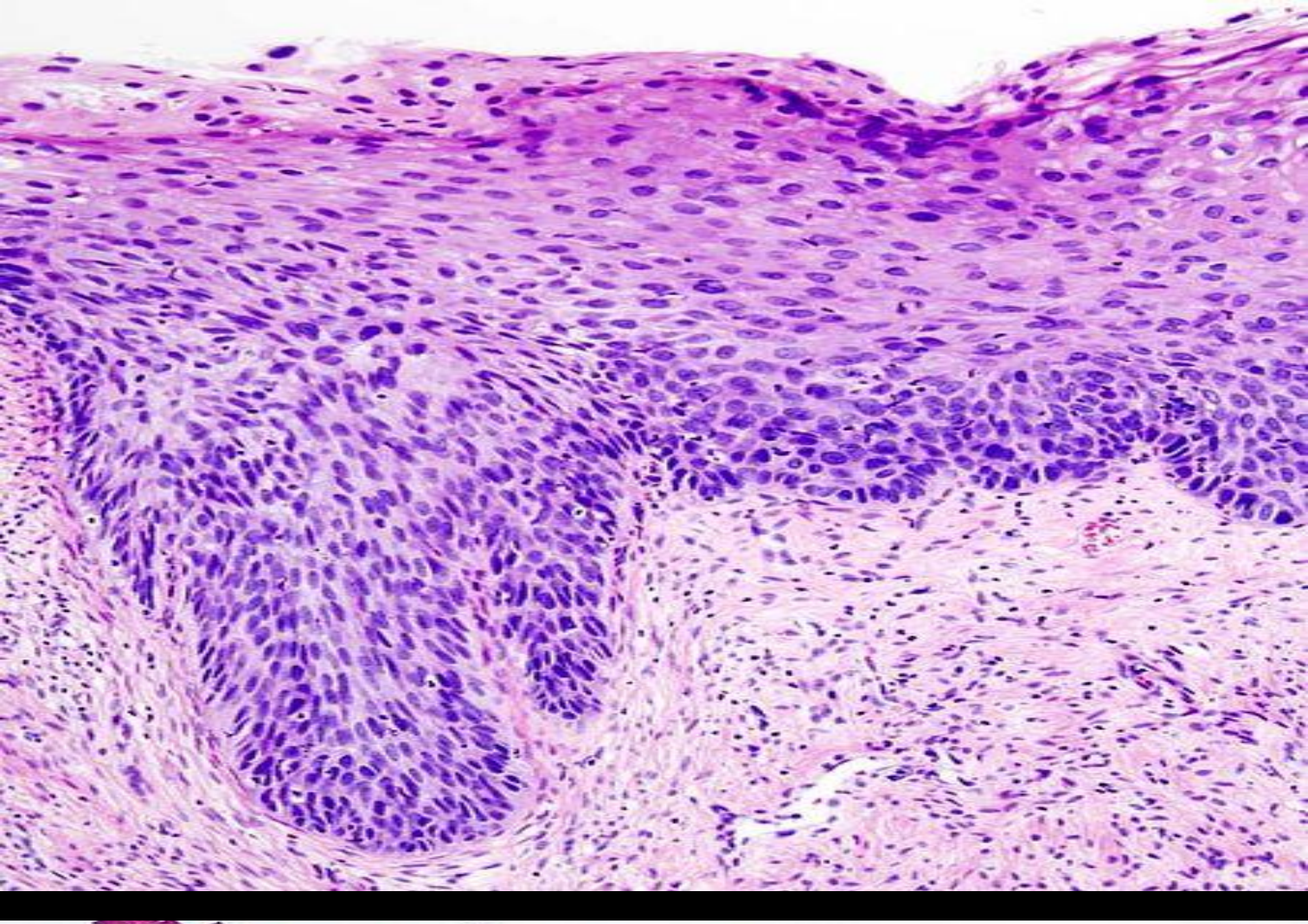
• If dysplastic changes involve the entire thickness of the epithelium it is called: carcinoma in-situ.

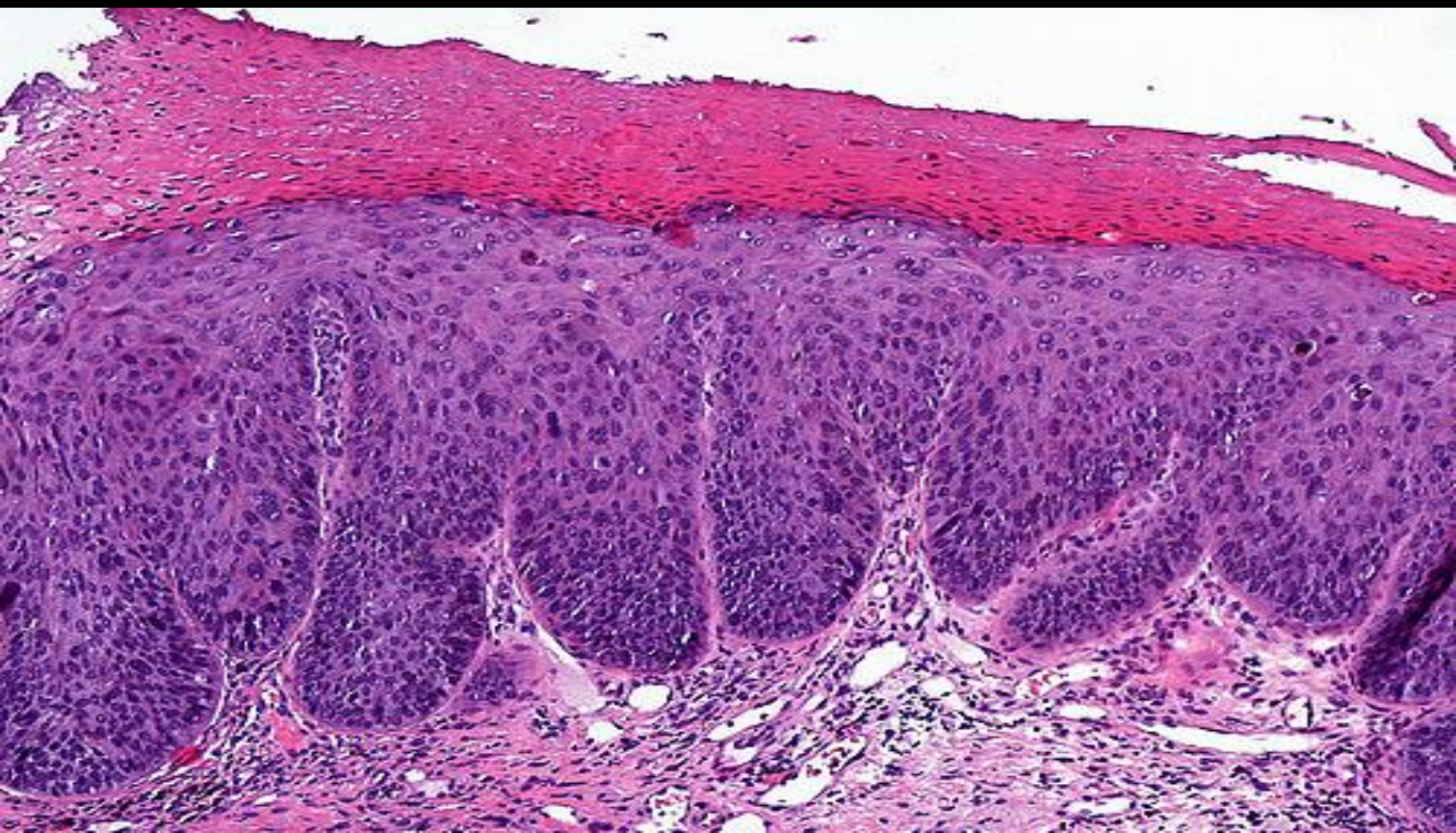
• Definition: an intraepithelial malignancy in which malignant cells involve the entire thickness of the epithelium without penetration* of the basement membrane

Some important points that you need to know :

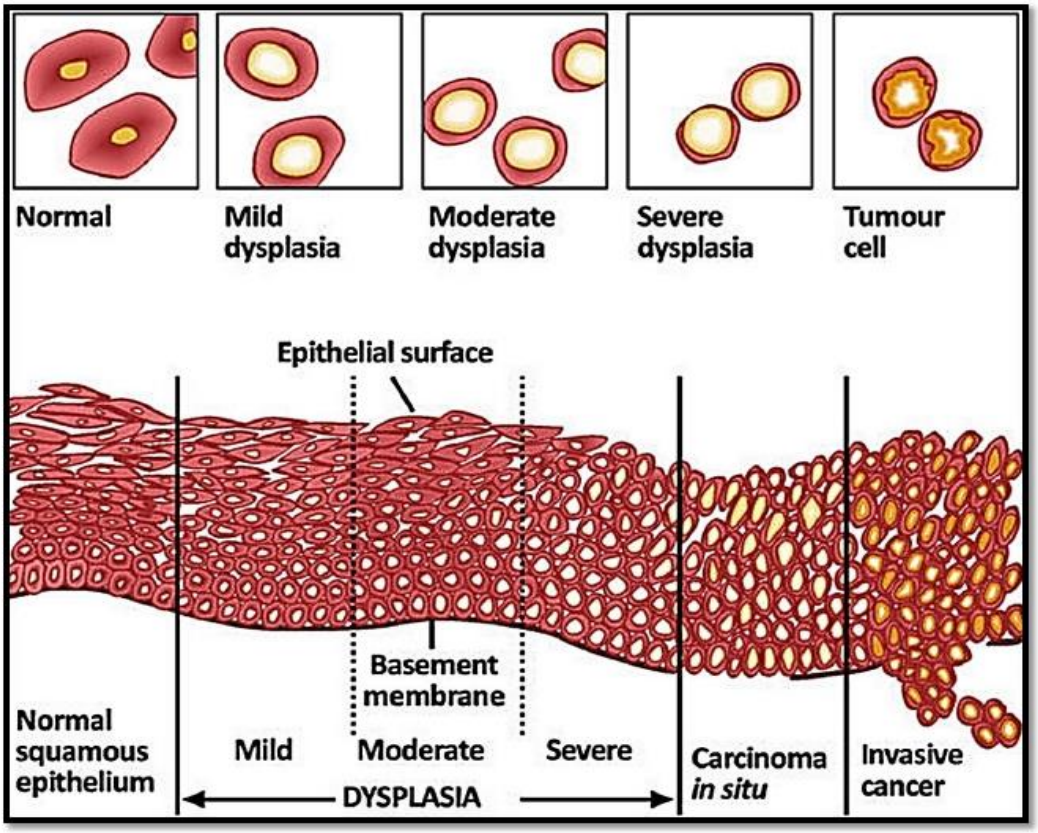
- It is applicable only to **epithelial** neoplasms.
- It is a true neoplasm with all of the features of malignant neoplasm except invasiveness**. (هنا قصده انه ورم حقيقي مثله مثل اي ورم خبيث ثاني و لكنه لا ينتشر في الجسم)
- It displays the cytological features of malignancy without invading the basement membrane.

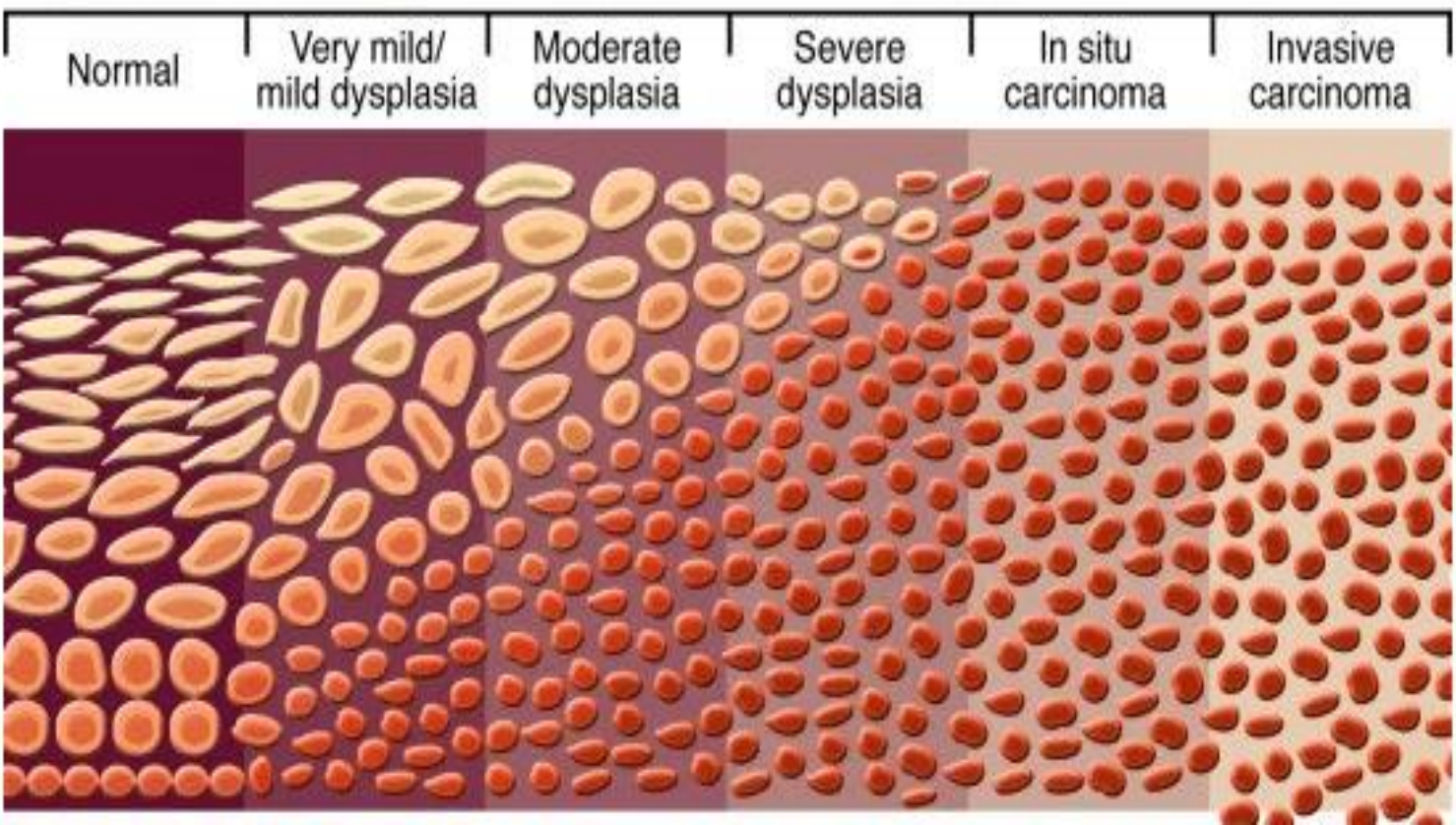
* Penetration : اختراق **Invasiveness : معناها غزو و المقصود فيها هو نفس ما ذكر اعلاه





Dysplasia & Carcinoma in Situ





MCQS

- **1) Anaplasia means ?**
- A) Poorly differentiated
- B) Moderately differentiated
- C) Undifferentiated .
- D) well differentiated

- **2 In well-differentiated benign tumors, mitoses will be usually ?**
- a) common
- b) rare .

- **3) In the histological examination of a tumor you should look for ?**
- a) Giant cells .
- b) normal mitosis.
- c) low nuclear/ cytoplasm ratio
- D) hypochromic

- **4) which of the following is characteristics of Benign tumors ?**
- A) the ability to compress it surrounding's
- b) the ability to invade it surroundings
- c) grows faster
- d) their growth is not effected by stroma

- **5) which of the following is most frequently involved secondary sites?**
- a) hart and kidney .
- b). liver and lungs
- c) Appendix
- d). Breast

- **6)Which of the following is the favorite way for carcinomas to spread ?**
- A) Hematogenous way
- B). Using the blood vessels
- C) .Using the body cavities
- D) Lymphatic way

- **7)Which of the following is more commonly invaded in the Hematogenous spreading** ?

- a) arteries
- b) Veins

- **8) Carcinoma in-situ is a true neoplasm with all of the features of malignant**
- **neoplasm except ?**

- a) high N/C ratio
- B) Hyperchrmasia
- c) abnormal Mitosis
- D) invasiveness

1. C
2. B
3. A
4. A
5. B
6. D
7. B
8. D

HOST DEFENSE AGAINST TUMORS

- **Tumor antigens:**

- **Tumor-specific antigens**: which are present **only** on **tumor** cells and not on any normal cells.

- **Tumor-associated antigens**,:which are present on **tumor** cells and also on some **normal** cells.

(you can detect them either in blood or tissue sample by special stain)

tumor cells imply genes in their surface so the body could recognise them and kill them.. but some of them can hide.

- **Classes of tumor antigens:Where do they come from?**

• Products of **mutated** oncogenes and tumor suppressor genes Know the examples*

- **P53** tumor suppressor gene, **RAS** oncogene these mutations will be expressed on the surface of the cell and then recognized as nonself and will be attacked by the immune mechanism

• Products of **amplified** genes

- HER2-NEU

• Tumor antigens produced by **oncogenic viruses**

which incorporates itself with the host DNA, theresulting proteins will be expressed on the cell membrane

- HPV, EBV

• **Oncofetal antigens**:

expressed during embryogenesis but not in normal adult tissues.

- CEA, AFP in colon and liver carcinomas, respectively.

• **Cell type–specific differentiation antigens**:

Tumors express molecules that normally are present on the cells of origin. These antigens are called differentiation antigens, because they are specific for particular lineages or differentiation stages of various cell type.Antigens (proteins) secreted by normal tissue and the tumors arising from this tissue

.

- **PSA[prostate specific antigen]** in prostatic carcinoma

Usually present late.. we look for PSA in blood if it's highly increased the patient will most likely have cancer

Antitumor effector mechanisms :

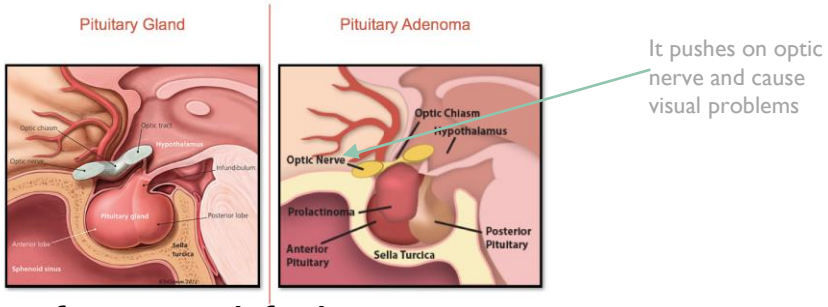
- **Cytotoxic T lymphocytes** Most efficient for killing cancer
- **Natural killer cells**
- **Macrophages**
- **Humoral mechanisms:**
  - Complement system
  - Antibodies

CLINICAL ASPECTS OF NEOPLASIA

- **Both malignant & benign tumors may cause problems because of:**

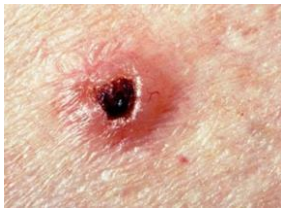
➢ **Location and impingement on adjacent structures:**

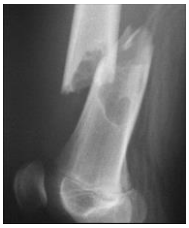
- Location is crucial in both benign and malignant tumors.
- A small (1-cm) **pituitary adenoma** can compress and destroy the surrounding normal gland, giving rise to **hypopituitarism**.
- A 0.5-cm **leiomyoma** (benign tumor of the smooth muscle) in the wall of the renal artery may encroach on the blood supply, leading to renal **ischemia** **and** **hypertension.**



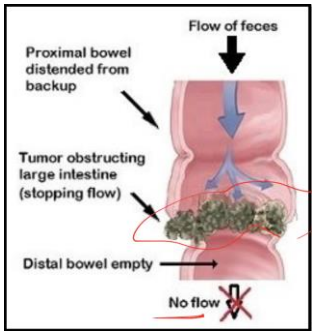
➢ **Bleeding, secondary fractures or infections:**

- A tumor may ulcerate through a surface or adjacent structures causing consequent bleeding or secondary infection or fracture (pathological fracture).





➢ **Symptomsthat result from rupture, obstruction or infarction Swelling and fever, huge mass effect**



➢ **Functional activity such as hormone synthesis or the development of paraneoplastic syndromes**

CLINICAL ASPECTS OF NEOPLASIA

➢ Example of Functional activity such as hormone synthesis:

- Hormone production is seen with benign and malignant neoplasms arising in endocrine glands.
- Adenomas and carcinomas arising in the beta cells of the **pancreatic islets of Langerhans** can produce **hyperinsulinism**, sometimes fatal.
- Some adenomas and carcinomas of the **adrenal cortex** elaborate corticosteroids that affect the patient (e.g., aldosterone, which induces sodium retention, hypertension, and hypokalemia).
- Such hormonal activity is **more likely** with a well-differentiated benign tumor than with a corresponding carcinoma.

adenomas

CLINICAL ASPECTS OF NEOPLASIA

- **Cancer Cachexia**: It is usually accompanied by:
  - Weakness
  - Anorexia
  - Anemia

- The **severity** of cachexia is generally correlated with the **size** and extend of **spread** of the cancer.

- The **origin of cancer cachexia** is multifactorial:

1. Anorexia (reduced calorie intake): ***TNF*** suppresses appetite
2. Increased basal metabolic rate & calorie expenditure
3. General metabolic disturbance. (the body gets the glucose but it does not metabolize it fully →
4. accumulation of glucose (used as a base for diagnosis)

usually patients have loss of appetite and the basal metabolic rate is high [rapid loss of wight]). in a normal state if a person goes on a diet then the basal metabolic rate is high in the first few days but then it reduces by time and goes back to normal.

Paraneoplastic syndromes:

- They are symptoms that occur in cancer patients and cannot be explained.
- They are diverse and are associated with many different tumors.
- They appear in 10% to 15% of patients.
- They may represent the earliest manifestation of an occult neoplasm.
  مثلاً مرض هوجكن يصير عند المريض حكه مالها سبب وبعد سنه يكتشفون ان عنده سرطان

- They may represent significant clinical problems and may be lethal.
- They may mimic metastatic disease.

-The most common **Paraneoplastic** syndromes are: (Hypercalcemia - Cushing syndrome-Nonbacterial thrombotic endocarditis)

-The most often neoplasms associated with these syndromes:
- **Lung** and **breast** cancers and **hematologic** malignancies.

Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	Small cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T cell leukemia/lymphoma Ovarian carcinoma	Parathyroid hormone–related protein, TGF-α, TNF, IL-1
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Hepatocellular carcinoma	Insulin or insulin-like substance
Carcinoid syndrome	Bronchial adenoma (carcinoid) Pancreatic carcinoma Gastric carcinoma	Serotonin, bradykinin
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
Nerve and Muscle Syndrome		
Myasthenia	Bronchogenic carcinoma, thymoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma, teratoma	
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic and breast carcinoma	Immunologic
Osseous, Articular, and Soft Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymoma	Immunologic
Others		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

GRADING AND STAGING OF CANCER

- **Grading:** It is based on the cytologic **differentiation** of tumor cells and the **number of mitoses** within the tumor.

- Tumors are classified as:
  - **Grade** I: well differentiated
  - **Grade** II: moderately differentiated
  - **Grade** III: poorly differentiated
  - **Grade** IV: anaplastic (undifferentiated)

- **Staging** is based on:
  1. the **size** of the primary lesion
  2. its extent of **spread** to regional lymph nodes
  3. the presence or absence of **metastases**.

-**poorly differentiated** neoplasms have cells that are **difficult to recognize** as to their cell of Origin.

- **Higher grade** means a **lesser degree of differentiation** and the **worse** the **biologic behavior.**
- - **A well differentiated neoplasm** is composed of cells that **closely resemble the cell of origin.**

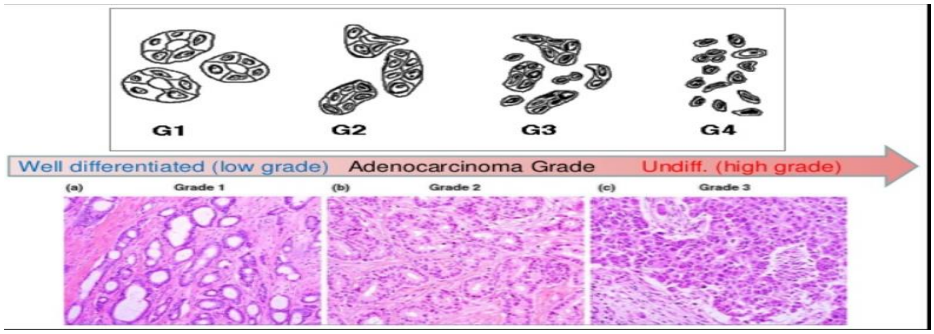
- **Two methods** of staging are currently in use:
  1. The **TNM** System (T, primary tumor, N, regional lymph node involvement; M, Metastases)
  2. The **AJC** System (American Joint Committee).

- **TNM Staging system:**
- T0, Tis(Tumor in situ), T1, T2, T3 and T4: describe the increasing **size** of the primary lesion.
- N0, N1, N2, and N3: indicate progressively advancing **node** involvement.
- M0 and M1: reflect the absence or presence, respectively, of distant **metastases**.

GRADING AND STAGING OF CANCER

Note: This is for understanding

Grading



Staging

Staging of Malignant Neoplasms	
Stage	**Definition**
Tis	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present

LABORATORY DIAGNOSING

A. Morphologic methods.

B. Biochemical assays: مثال لو شخص سوينا له عملية ازالة ورم يختفي االنتيجين حق الورم بعدين اسوي له تحاليل كل فترة عشان اشوف الجين رجع او ال

- Useful for measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum.
- Useful in determining the effectiveness of therapy and detection of recurrences after excision.
- Elevated levels may not be diagnostic of cancer (PSA). **(prostatic specific antigen)**
- Only few tumor markers are proved to be clinically useful, example CEA and α- fetoprotein.

C. Molecular diagnosis:

(to identify genetic material changes e.g: translocation - deletion ,prognosis and modification of treatment)

- **Polymerase chain reaction (PCR):**

Example: detection of **BCR-ABL** transcripts in chronic myeloid leukemia.

- **Fluorescent in situ hybridization (fish):**

it is useful for detecting chromosomal translocation characteristic of many tumors

Both PCR and Fish can show amplification of oncogenes (HER2 and N-MYC)

D. Microscopic Tissue Diagnosis

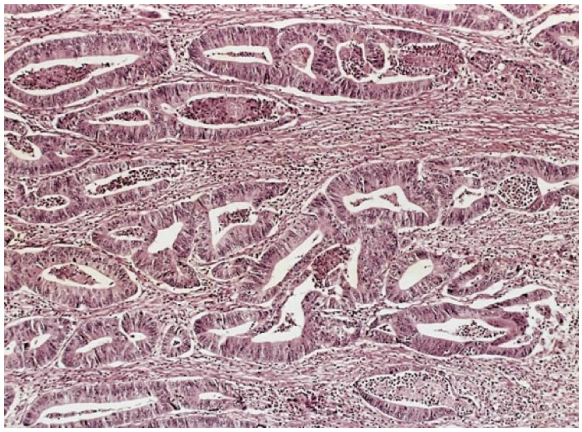
1. The gold standard of cancer diagnosis.
2. Several sampling approaches are available:

-**Excision** (removal of whole organ) or **biopsy**.

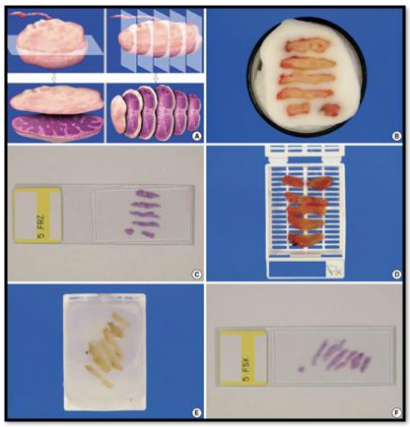
- **Frozen section.** (quick diagnosing):a method in which a sample is quick-frozen and sectioned, permits histologic evaluation within minutes.

-**fine-needle aspiration:** it involves aspiration of cells from a mass, followed by cytologic examination of the smear.

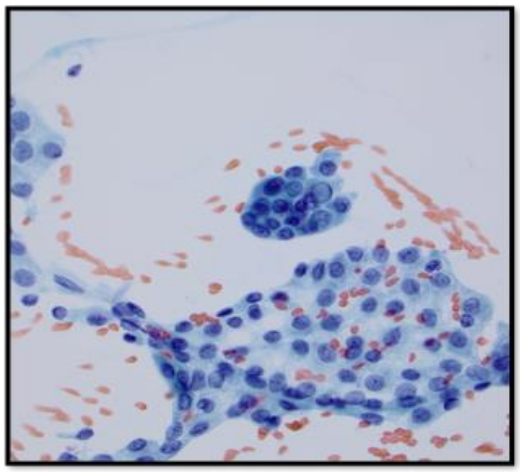
- **Cytologic (Papanicolaou) smears**: provide another method for the detection of cancer. Neoplastic cells are less cohesive than others and are therefore shed into fluids or secretions.



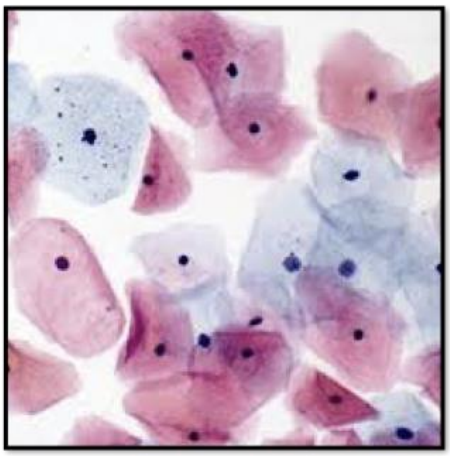
Histologic method



Frozen section.

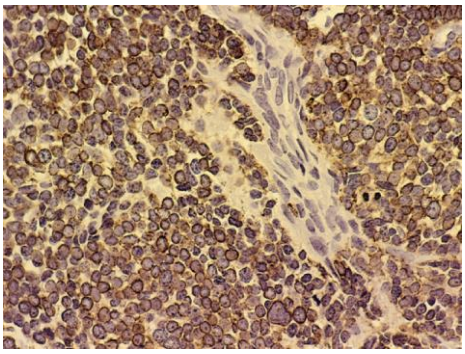


fine-needle aspiration

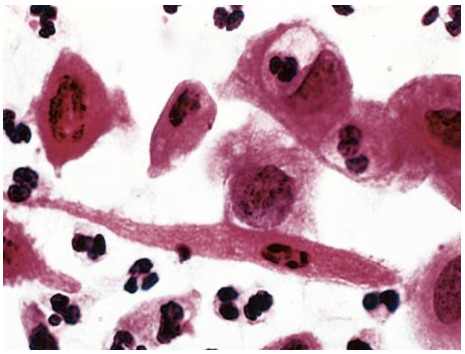


Cytologic (Papanicolaou) smears

LABORATORY DIAGNOSING



Immunohistochemistry (antigen antibody reactions) if the tissue is extremely undifferentiated then we put antibodies and look for positive reactions with the antigens , these antigenic expressions specify exactly which cancer cell it is *the dark parts are positive and the light ones are negative



Cytopathology

- **DNA microarray analysis:**
- Expression of thousands of genes are studied.
- Different tissue has different pattern of gene expression.
- Powerful tool useful for subcategorization of disease e.g. Lymphoma
  - confirmation of morphologic diagnosis
  - illustration of genes involved in certain disease and possible therapy.

WHAT IS CARCINOGENESIS ?

- **Carcinogenesis** is a multistep process at both the phenotypic and the genetic levels.
- It starts with genetic damage:

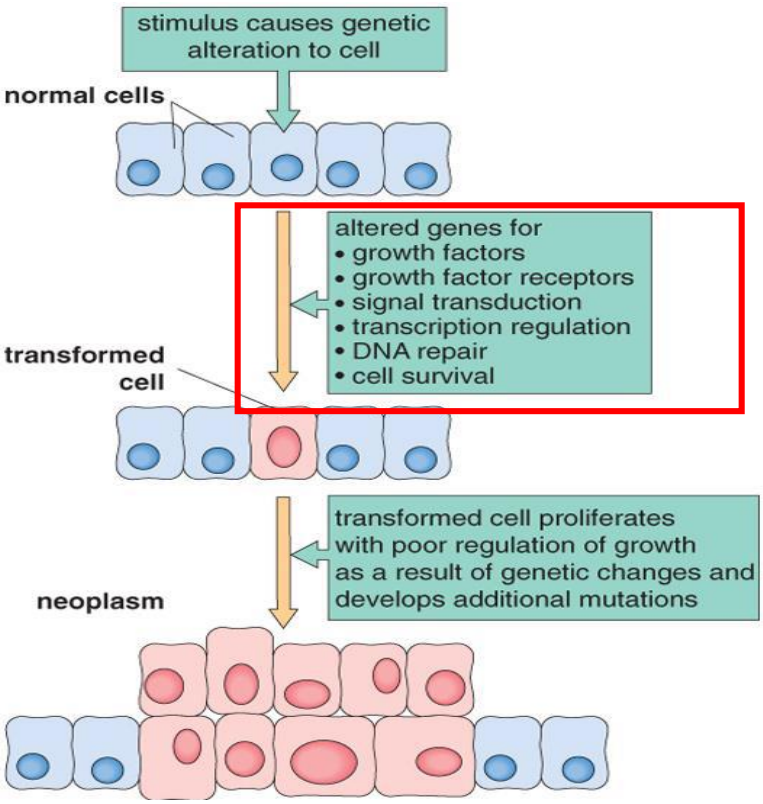
  1- Environmental:

  - Chemical
  - Radiation
  - Infectious

  2- Inherited

- Genetic damage leads to "mutation"
- Single cell which has the genetic damage undergoes neoplastic proliferation (**clonal expansion**) forming the tumor mass. (**Monoclonal**)
  - Cancer is **Monoclonal** while - for example - Hyperplasia is **Polyclonal**.

  -**Monoclonal** means that only one defective cell in needed to produce the cancer.



التغيرات الجينية التي تحدث

WHERE ARE THE TARGETS OF THE GENETIC DAMAGE?

- Four regulatory genes are the main targets:

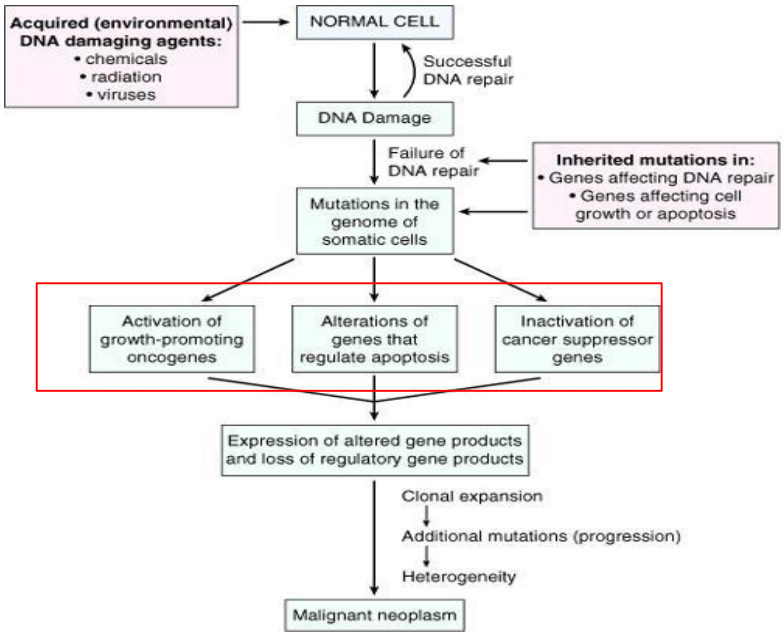
- Growth promoting proto-oncogenes
  Proto-oncogene > mutation > oncogene
- Growth inhibiting (suppressor) genes
- Genes regulating apoptosis
- DNA repair genes

1) **proto-oncogenes**. The "**accelerators**" that are responsible for the cell growth/

Do you think there will be a loss of function or gain of function mutation? Since cancer cells grow quickly these genes must be overexpressed, having a gain of function mutation. **Proto-oncogene → mutation → oncogene**

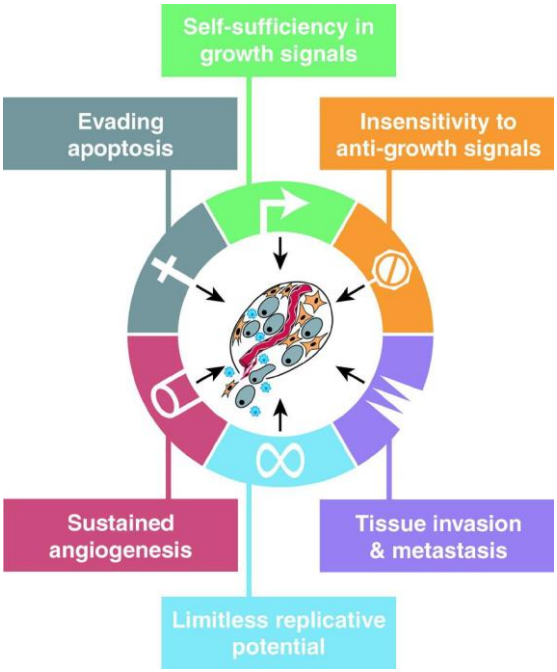
2) **Tumor suppressor genes**. The "**breaks**" that inhibit the cell growth/

Do you think these genes will have gain of function or loss of function mutation? Since cancer cells' break system is not working, these genes must have a loss of function mutation.



CARCINOGENESIS

- Main changes in the cell physiology that lead to formation of the malignant phenotype:

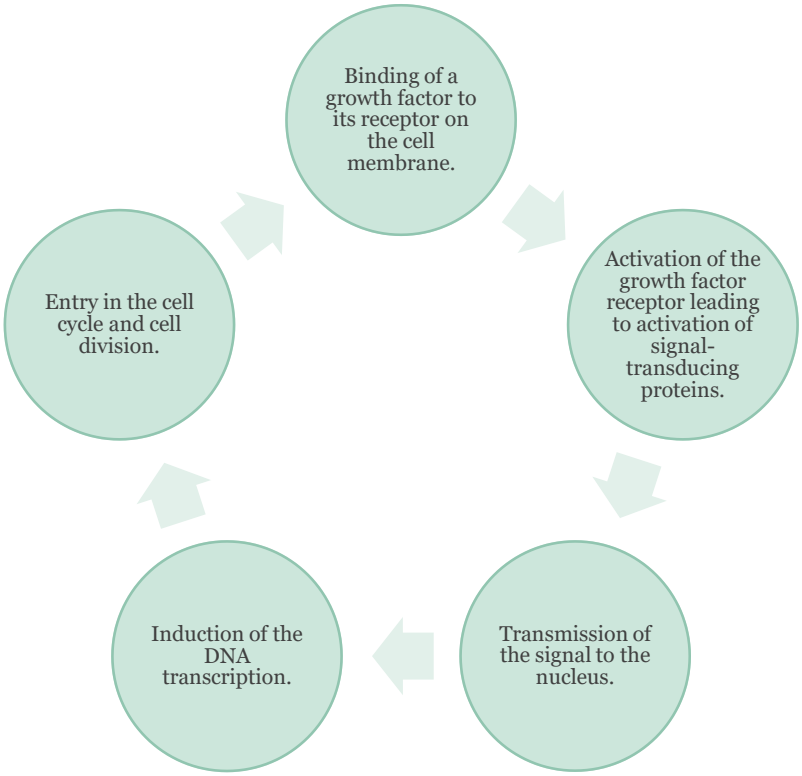


Note: These occur progressively.

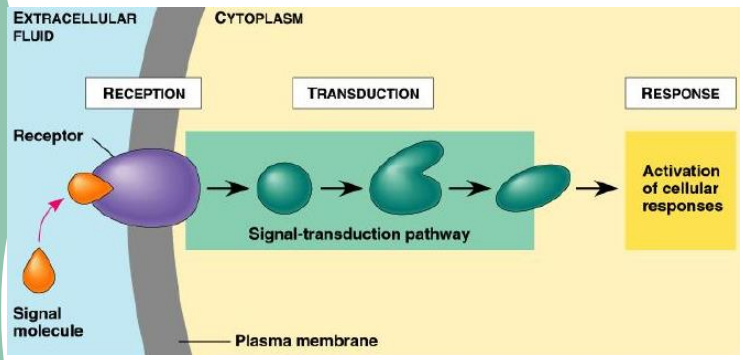
A- SELF-SUFFICIENCY IN GROWTH SIGNALS:

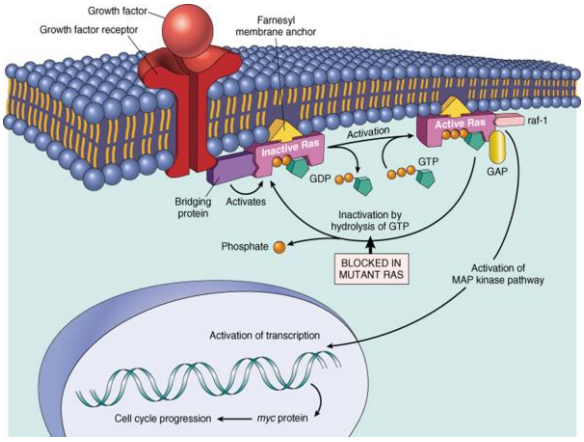
- **Oncogene** (abnormal): a gene that promotes autonomous cell growth in cancer cells.
  - Derived by mutations in **proto-oncogenes** (normal).
  - Characterized by the ability to promote cell growth in the absence of normal growth-promoting signals.
- **Onco-proteins**: are the products of this process.

- **Remember the cell cycle!**



Note:
Any mutation of the previous steps can cause neoplastic transformation.





HOW DO CANCER CELLS ACQUIRE SELF-SUFFICIENCY IN GROWTH SIGNALS?

- **1- Growth factors:**
  - Cancer cells are capable of synthesizing the same growth factors to which they are responsive. i.e. **causes autonomous stimulation.**
    - Sarcomas → TGF-a
    - Glioblastoma → PDGF (platelet derived growth factor)

*__Platelet-derived growth factor (PDGF) i__s one of the numerous growth factors, or proteins that regulate cell growth and division. In particular, it plays a significant role in blood vessel formation (angiogenesis), the growth of blood vessels from already-existing blood vessel tissue. Uncontrolled angiogenesis is a characteristic of cancer.

*__Glioblastoma__ is the most common and most aggressive malignant primary brain tumor in humans, involving glial cells and accounting for 52% of all functional tissue brain tumor cases and 20% of all intracranial tumors.

- **2- Growth factors receptors:**
  - **Mutation**:

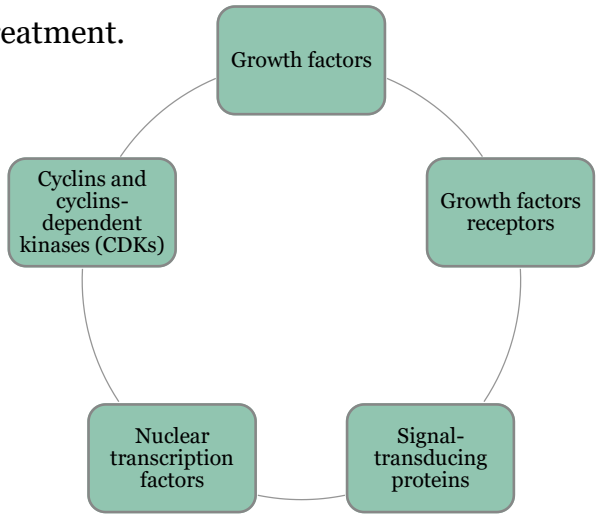
    -Continuous signals to cells and uncontrolled growth.

    -Signals become amplified.
  - **Overexpression**:

    -Cells become very sensitive thus becoming hyper-responsive to normal levels of growth factors.

Epidermal Growth Factor (EGF) Receptor family:

- HER2
  - Amplified in breast cancers and other tumors.
  - High levels of HER2 in **breast cancer** indicate **poor prognosis**.
  - Anti- HER2 antibodies are used in treatment.



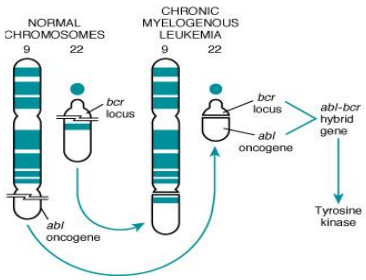
3- Signal-transducing proteins : (signaling pathway inside the cytoplasm)

- They receive signals from activated growth factors receptors and transmit them to the nucleus.
- Happens in the cytosol and causes continuous messaging.
- Examples :
  - RAS
  - ABL

RAS:
- 30% of all human tumors contain mutated RAS gene .
- E.g.: colon cancer. Pancreas cancers
- Mutations of the RAS gene is the most common oncogene abnormality in human tumors
- Mutations in RAS → cells continue to proliferate

ABL gene:
- ABL proto-oncogene has a tyrosine kinase activity
- Its activity is controlled by negative regulatory mechanism
- E.g.: chronic myeloid leukemia (CML):
  - t(9,22) Philadelphia translocation → ABL gene transferred from ch.9 to ch.22
  - Fusion with BCR → BCR-ABL
  - BCR-ABL has tyrosine kinase activity (oncogene)

CML patients are treated with (Gleevec) which is inhibitor of ABL kinase



4- Nuclear transcription factors :

- Mutations may affect genes that regulate transcription of DNA → growth autonomy.
- e.g. MYC
  - MYC proto-oncogene produce MYC protein when cell receives growth signals.
  - MYC protein binds to **DNA** leading to activation of growth-related genes.
- Normally MYC decrease when cell cycle begins, but in tumors there is sustained expression of MYC → continuous proliferation.
- e.g. Burkitt Lymphoma ; MYC is dysregulated due to t(8,14).

5- Cyclins and cyclins- dependent kinases (CDKs)

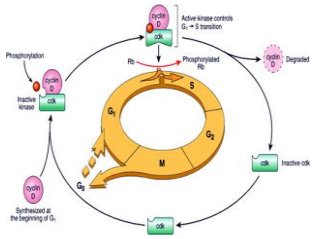
Progression of cells through cell cycles is regulated by CDKs after they are activated by binding with cyclins.

Mutations that dysregulate cyclins and CDKs will lead to cell proliferation.

Example:

-Cyclin D genes are overexpressed in breast, esophagus, and liver cancers.

-CDK4 is amplified in melanoma and sarcomas.



B- INSENSITIVITY TO GROWTH-INHIBITORY SIGNALS

- Tumor suppressor genes control (apply brakes) cells proliferation
- If mutation caused disruption to them → cell becomes insensitive to growth inhibition → uncontrolled proliferation
- Both Tumour suppressor genes must be inactive to cause insensitivity
- e.g. RB, TGF-b, APC, P53.

Extra Explanation:

P53 (Very Important)

P53 induced apoptosis of cell with irreversible DNA damage is the ultimate protective mechanism against neoplastic.

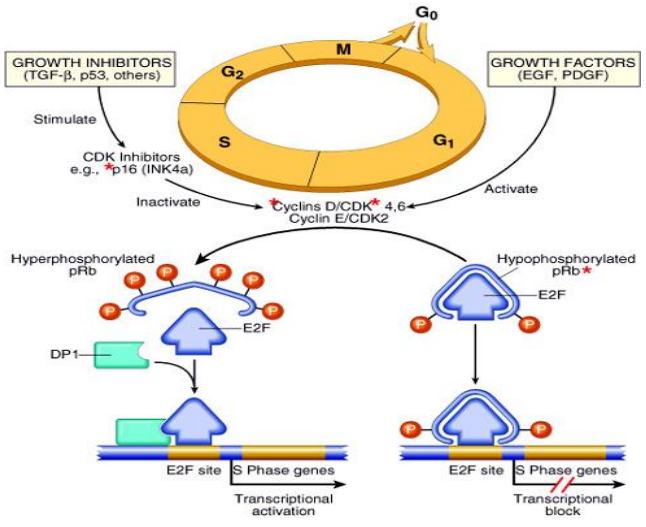
To summarize p53 it's activated by stress such as DNA damage or assist in DNA repair causing G1 arrest and inducing DNA repair genes.

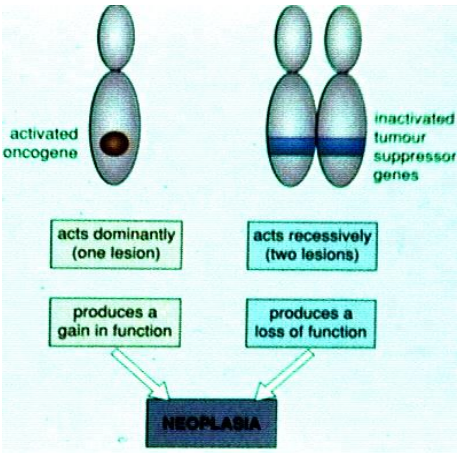
P53 direct a cell with damaged DNA (irreversibly) or senescence* to go under apoptosis.

Senescence mean loss of cell power of division or growth.

Note:

BAX (apoptosis gene) helps with the apoptosis process

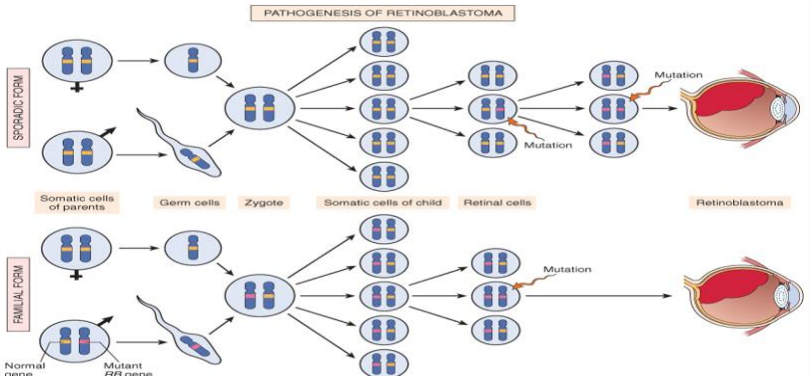




TUMOR SUPPRESSOR GENES

- **RB (retinoblastoma) gene**
  - First tumor suppressor gene discovered. It was discovered initially in retinoblastomas.
  - Found in other tumors, e.g. breast cancer.
  - is a **DNA-binding** protein located on **chromosome 13.**
  - **RB** gene exists in " **active** " and " **inactive**" forms.
  - If **active** → will stop the advancing from **G1** to **S** phase in cell cycle.
  - If cell is stimulated by growth factors → inactivation of RB gene → brake is released → cells start cell cycle …G1 → S → M …then RB gene is activated again.

- **Retinoblastoma** is an uncommon childhood tumor.
  - Retinoblastoma is either **sporadic (60%) or familial (40%).**
  - **Two mutations** required to produce retinoblastoma.
  - Both normal copies of the gene should be lost to produce retinoblastoma.

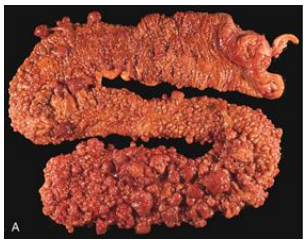


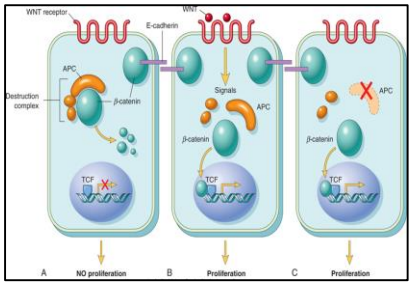
- **Transforming Growth Factor- b pathway (TGF-b):**
  - **TGF-b** is an inhibitor of proliferation.
  - It regulate **RB** pathway.
  - Inactivation of **TGF-b** lead to cell proliferation.
  - Mutations in **TGF-b** pathway are present in:
    - 100% of pancreatic cancers.
    - 83% of colon cancers.

TUMOR SUPPRESSOR GENES CONT.

Adenomatous Polyposis Coli – b Catenin (APC) pathway:

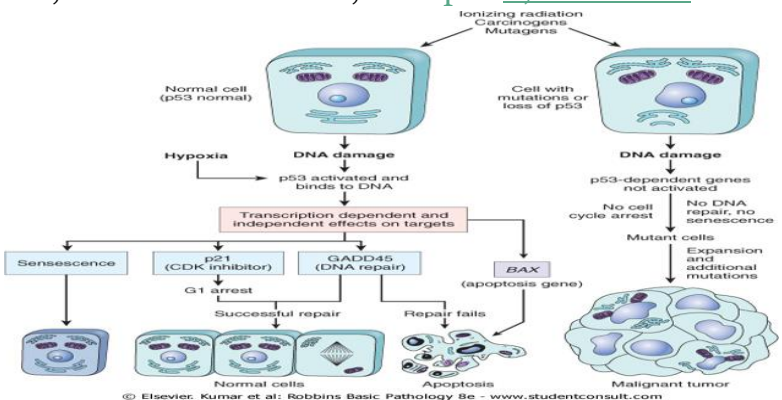
- **APC** is tumor **suppressor gene.**
- **APC** gene loss is very common in **colon cancers.**
- It has anti-proliferative action through inhibition of b-Catenin which activate cell proliferation.
- Individuals with mutant APC develop **colonic polyposis.**
- One or more of the polyps will progress to colonic carcinoma.
- **Treatment: Total Colectomy.**
- APC mutations are seen in 70% to 80% of **sporadic** colon cancers.





P53

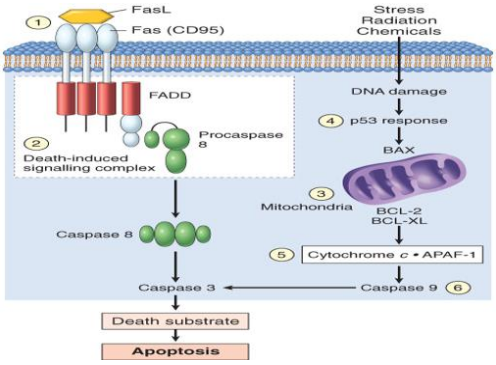
- It has multiple functions, mainly: Tumor suppressor gene (anti-proliferative).
- Regulates apoptosis.
- P53 senses DNA damage and causes G1 arrest to give chance for DNA repair (induces DNA repair genes).
- If a cell with damaged DNA cannot be repaired, it will be directed by P53 to undergo apoptosis.y
- With loss of P53, DNA damage goes unrepaired, thus mutations will be fixed in the dividing cells, leading to malignant transformation.
- P53 is called the ***"guardian of the genome".***
- 70% of human cancers have a defect in P53, it has been reported with almost all types of cancers: e.g. Lung. colon, breast.
- In most cases, mutations are acquired, but can be inherited, example: L,i-Fraumeni syndrome.



C- EVASION OF APOPTOSIS

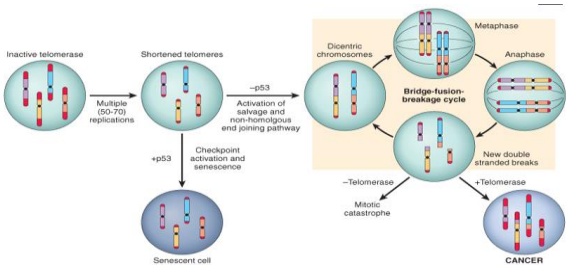
- Mutations in the **genes regulating apoptosis** are factors in malignant transformation.
- Cell survival is controlled by genes that promote and inhibit apoptosis.
- Reduced **CD95** level inactivate death – induced signaling cascade that cleaves DNA to cause death → tumor cells are less susceptible to apoptosis.
- DNA damage induced apoptosis (with the action of P53) can be blocked in tumors.
- **loss** of **P53** and up-regulation of **BCL2** prevent apoptosis.
  - Example: follicyular lymphoma

BCL2 is an anti-apoptosis family



D- LIMITLESS REPLICATIVE POTENTIAL

- Normally there is progressive **shortening of telomeres** at the ends of chromosomes.
- **Telomerase** is active in normal stem cells but absent in somatic cells.
- In **tumor cells :** activation of the enzyme telomerase, which can maintain normal telomere length.
  - Thus causing the **limitless replication as the telomeres are not being worn down.**

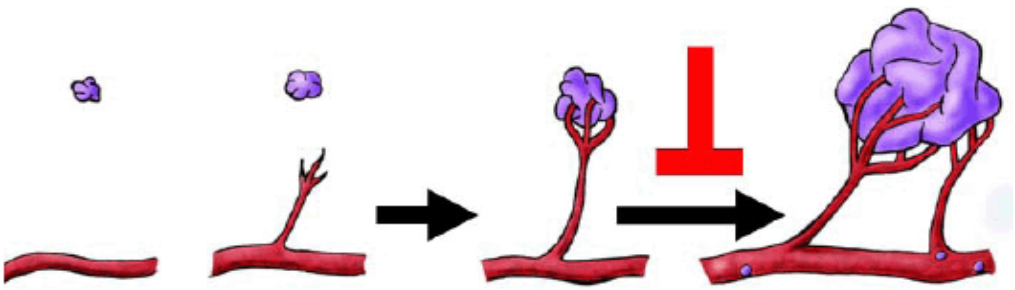


A telomere is a region of repetitive nucleotide sequences at each end of a chromatid, which protects the end of the chromosome from deterioration or from fusion with neighbouring chromosomes. During chromosome replication, the enzymes that duplicate DNA cannot continue their duplication all the way to the end of a chromosome, so in each duplication the end of the chromosome is shortened[1] (this is because the synthesis of Okazaki fragments requires RNA primers attaching ahead on the lagging strand). The telomeres are disposable buffers at the ends of chromosomes which are truncated during cell division; their presence protects the genes before them on the chromosome from being truncated instead. In normal cells, when the te lomere is exhausted (eaten up) the cell stops DNA synthesis because it might damage the cell's DNA. Cancer cells seem to have telomerases, enzymes that create telomeres; which gives them this high replicative capacity.

E-SUSTAINED ANGIOGENESIS

- Neovascularization has two main effects:
  - Perfusion supplies oxygen and nutrients.
  - Newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors, e.g. PDGF, IL-1.
- Angiogenesis is required for metastasis.

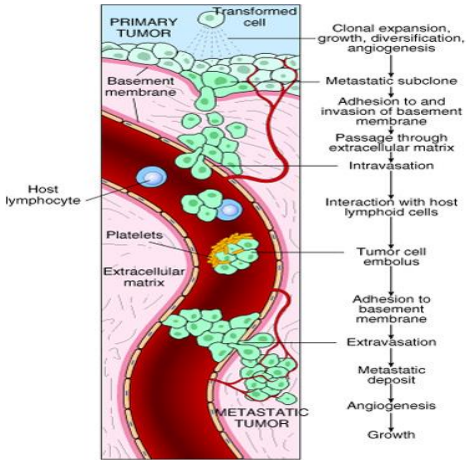
- **How do tumors develop a blood supply (Neoplastic angiogenesis)?**
  - Tumor-associated angiogenic factors.
    - These factors may be produced by tumor cells or by inflammatory cells infiltrating the tumor e.g. macrophages.
    - Important factors :
      - Vascular endothelial growth factor (VEGF)
      - Fibroblast growth factor



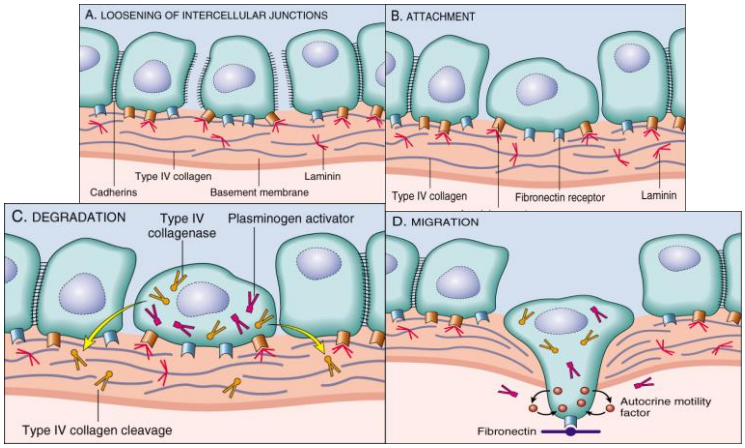
F- ABILITY TO INVADE AND METASTASIZE

- **Two phases** :
  - Invasion of extracellular matrix.
  - Vascular dissemination and homing of tumor cells.

- **invasion of ECM:**
  - Malignant cells first breach the underlying basement membrane.
  - Traverse the interstitial tissue.
  - Penetrate the vascular basement membrane.
  - Gain access to the circulation.



- Investorsn of the ECM has **four** steps:
  1. Detachment of tumor cells from each other.
  2. Attachments of tumor cells to matrix components.
  3. Degradation of ECM by collagenase enzyme.
  4. Migration of tumor cells.

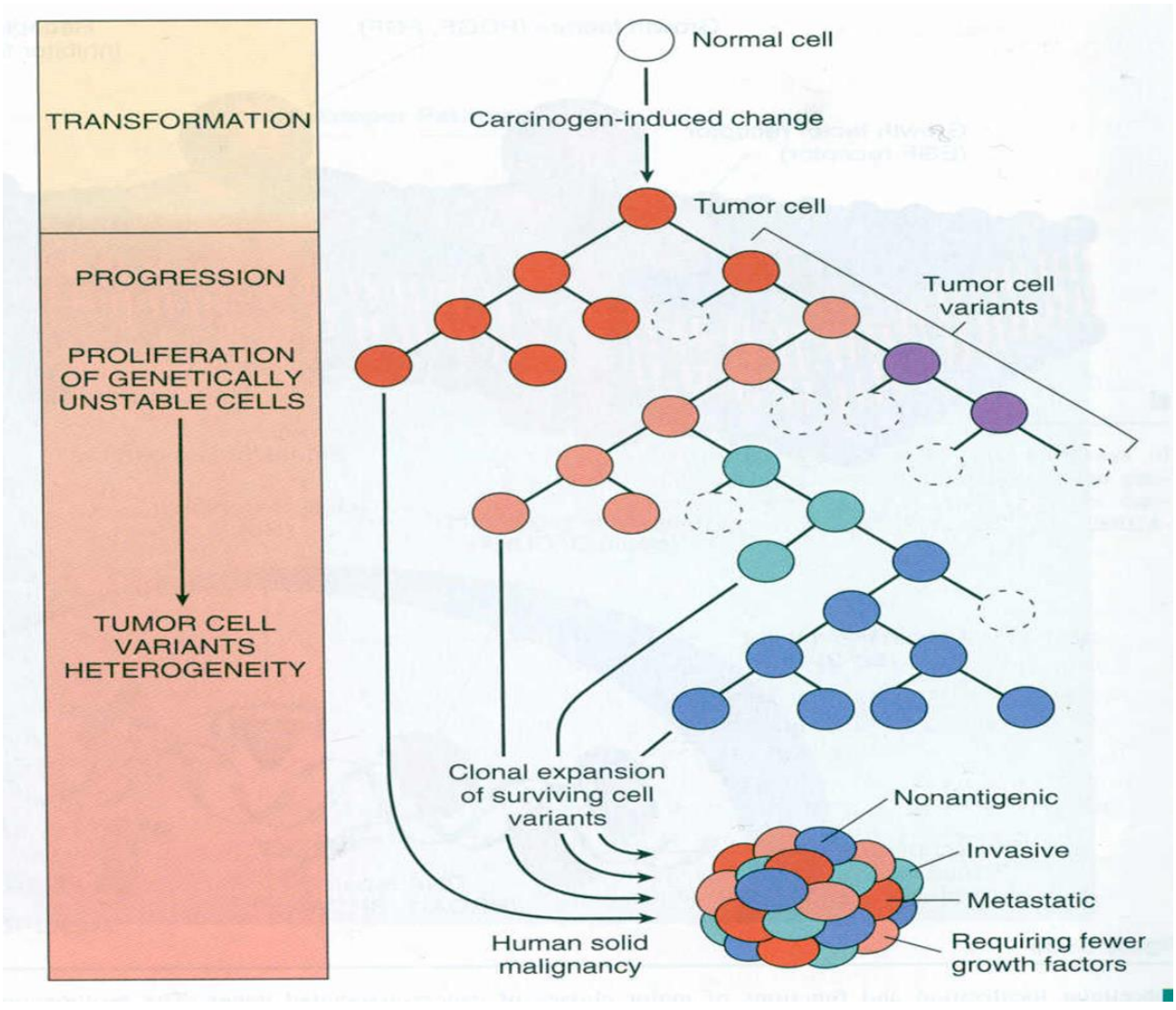


- **Vascular dissemination and homing of tumor cells:**
  - Most travel as single cells, they adhere to vascular endothelium and may form **emboli**.
  - Extravasation.

TUMOR PROGRESSION

- Many tumors become more aggressive and acquire greater malignant potential this is called “tumor progression” and is not necessarily an increase in size!
- With time, the tumor becomes clinically evident, their constituent cells are extremely heterogeneous غير متجانسة.

During progression: Tumor cells are subjected to immune and nonimmune selection pressures. For example, cells that are highly antigenic are destroyed by host defenses, whereas those with reduced growth factor requirements are positively selected.



Genomic Instability

- Enable of malignancy
- Due to defect in DNA repair genes

Examples:

-Hereditary Nonpolyposis colon carcinoma (HNPCC)
- Xeroderma pigmentosum →
- Familial breast cancer

It occurs when –When the genes are responsible of repair aren't working propperly/

Familial breast cancer:

- These genes regulate DNA repair
- Account for **80% of familial breast cancer**
- They are also involved in other malignancies
- Due to mutations in **BRCA1** and **BRCA2** genes.

Molecular Basis of multistep Carcinogenesis

- Cancer results from accumulation of multiple mutations
- all cancers have multiple genetic alterations, involving activation of several oncogenes and

loss of two or more tumor suppressor genes.

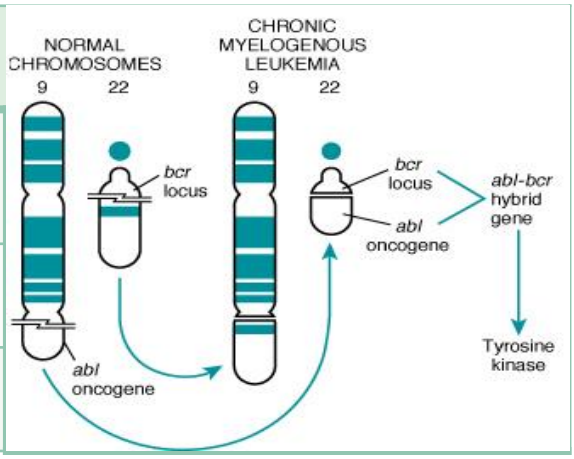
KARYOTYPIC CHANGES IN TUMORS

Translocations

In CML : t(9,22) " Philadelphia chromosome "

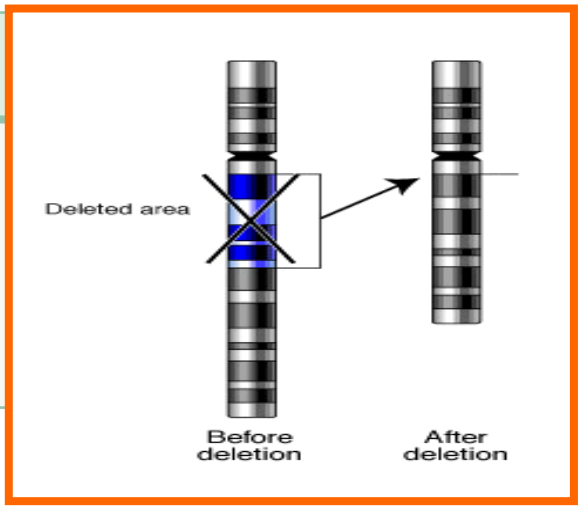
In Burkitt Lymphoma : t(8,14)

In Follicular Lymphoma : t(14,18)



Deletion

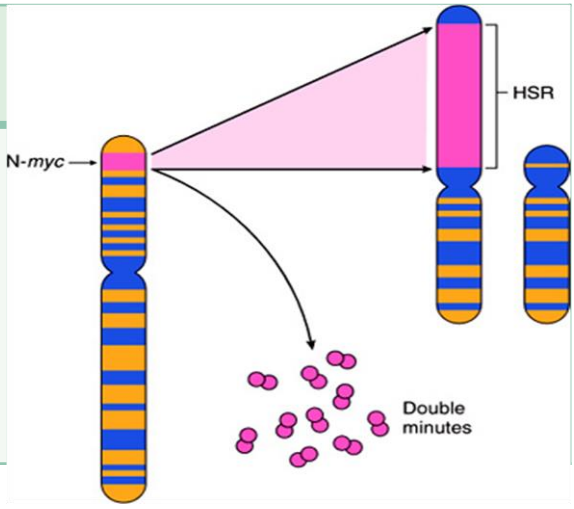
Chromosomal deletions are the second most prevalent karyotypic abnormality in tumor cells. Compared with translocations, For example: 1p36 deletion syndrome is caused by a deletion of genetic material from a specific region in the short (p) arm of chromosome 1



Gene amplification

Breast cancer : HER-2

HER2 (human epidermal growth factor receptor 2) is a gene that can play a role in the development of *breast cancer*. ... *Breast* cancers with *HER2* gene amplification or *HER2* protein overexpression are called *HER2*-positive



MCQS

- **1) Oncogene produces ?**
- a) Cystatin C
- b) protooncogenes
- c) Oncoproteins
- d) Amylase

- **2) Glioblastoma synthesize which growth factor(which they are respond to it)?**
- a) platelets derived growth factor.
- b) TGF-β
- c) EGF
- d) TGF-α

- **3) most common oncogene abnormality in human tumors?**
- a) RAS
- b) ABL
- c) EGF
- d) TGF-α

- **4) chronic myeloid leukemia(ABL) ?**
- a) t (8,14)
- b) t(9,22)
- c) t(8,22)
- d) t(9,14)

- **5) CML patients are treated with?**
- a) Anti- HER2 antibodies
- b).
- c) Gleevec
- d)

- **6) Burkitt's lymphoma (MYC is dysregulated due to) ?**
- a) t (8,14)
- b) t(9,22)
- c) t(8,22)
- d) t(9,14)

- **7)is called the " guardian of the genome"?**
- a). P53
- b) APC
- c) TGF-β
- d**)** RB

- **8)First tumor suppressor gene discovered and it is located on chromosome 13?**
- a). P53
- b) APC
- c) TGF-β
- d) RB

- **9)** 100% **of pancreatic cancers have Mutations in?**
- a). P53
- b) APC
- c) TGF-β
- d) RB

- **10) follicular lymphoma has ?**
- a) gain of P53 and down-regulation of BCL2
- b) loss of P53 and up-regulation of BCL2

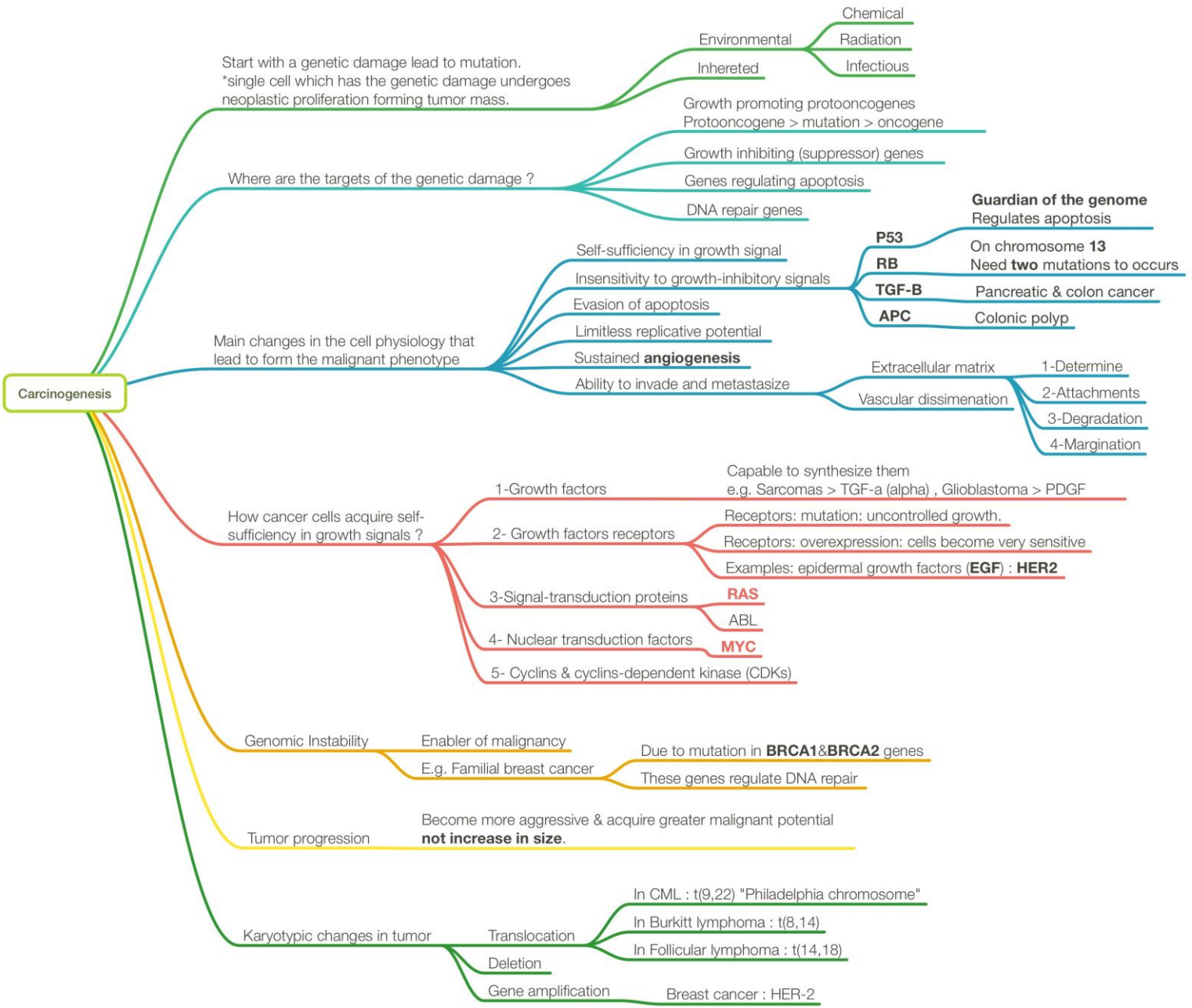
- **11) Telomerase is normally active in?**
- a) normal stem cells
- b) abnormal stem cells
- c) somatic cells

- **12) In Follicular Lymphoma(**Evasion of apoptosis) **?**
- a) t (8,14)
- b) t(14,18)
- c) t(8,22)
- d) t(9,14)

1. C
2. A
3. A
4. B
5. C
6. A
7. D
8. D
9. C
10. B
11. A
12. B

- Helpful videos:
  - Oncogenes: https://www.youtube.com/watch?v=QRPRmRAOCog
  - Tumor Suppressors: https://www.youtube.com/watch?v=XhSsMjuzt9Y
  - Molecular Basis of Carcinogenesis (explained by Dr. Rawan Altuwaijri from KSAU-HS): https://www.youtube.com/watch?v=w4w2VTQqyMM

SUMMARY


Carcinogenesis
Start with a genetic damage lead to mutation.
*single cell which has the genetic damage undergoes neoplastic proliferation forming tumor mass.
Environmental
Chemical
Radiation
Infectious
Inhereted
Where are the targets of the genetic damage ?
Growth promoting protooncogenes
Protooncogene > mutation > oncogene
Growth inhibiting (suppressor) genes
Genes regulating apoptosis
DNA repair genes
Main changes in the cell physiology that lead to form the malignant phenotype
Self-sufficiency in growth signal
Insensitivity to growth-inhibitory signals
P53
Guardian of the genome
Regulates apoptosis
RB
On chromosome 13
Need two mutations to occurs
TGF-B
Pancreatic & colon cancer
APC
Colonic polyp
Evasion of apoptosis
Limitless replicative potential
Sustained angiogenesis
Ability to invade and metastasize
Extracellular matrix
1-Determine
2-Attachments
Vascular dissimenation
3-Degradation
4-Margination
How cancer cells acquire self-sufficiency in growth signals ?
1-Growth factors
Capable to synthesize them
e.g. Sarcomas > TGF-a (alpha) , Glioblastoma > PDGF
2- Growth factors receptors
Receptors: mutation: uncontrolled growth.
Receptors: overexpression: cells become very sensitive
Examples: epidermal growth factors (EGF) : HER2
3-Signal-transduction proteins
RAS
ABL
4- Nuclear transduction factors
MYC
5- Cyclins & cyclins-dependent kinase (CDKs)
Genomic Instability
Enabler of malignancy
E.g. Familial breast cancer
Due to mutation in BRCA1&BRCA2 genes
These genes regulate DNA repair
Tumor progression
Become more aggressive & acquire greater malignant potential
not increase in size.
Karyotypic changes in tumor
Translocation
In CML : t(9,22) "Philadelphia chromosome"
In Burkitt lymphoma : t(8,14)
In Follicular lymphoma : t(14,18)
Deletion
Gene amplification
Breast cancer : HER-2

SUMMARY

Normal function in normal cells	Oncogene	Mutation	Disease	Treatment
Growth factors	TGF-α	Produced in	Sarcomas	
	PDGF	Produced in	Glioblastoma	
Growth factor receptors	HER-2(from EGF receptor family)	Amplified in	Breast cancer	Anti-HER2 antibodies
Signal transduction proteins	RAS	If mutated cells continue to proliferate	Colon , pancreatic cancers	
	ABL Has tyrosine activity	BCR-ABL Translocation t(9,22) (Philadelphia chromosome)	LMD (chronic myeloid leukemia)	Gleevec
Nuclear transcription factor	MYC	t(8,14) ,mostly by Epstein-Barr virus	Burkitt Lymphoma	
Cell cycle regulation	Cyclins	Cyclin D is amplified in	Breast,osophagus, liver cancer	
	CDKs :Cyclin Dependent Kinases	CDK4 is amplified in	-Melanoma -sarcomas	
Tumor suppressor genes	RB	Located in chromosome 13	- retinoblastoma (two mutations required to produce retinoblastoma) ,either familial or sporadic -breast cancer	
	TGF-β	mutated in	-100% all of pancreatic cancer -83% of colon cancer	
	APC : Adenomatous Polyposis Coli	mutated in	-Adenomatous polyposis in colon -colon cancer	
	P53 :regulate DNA repair + cell apoptosis	-acquired in most of cases -inherited: Li-Fraumeni syndrome (autosomal dominant)	Almost ALL types of cancers	
	BRCA1 BRCA2	mutated in	Familial breast cancer	
Evasion of Apoptosis	BCL2 (apoptosis inhibitor)	t(14:18) =overexpressed BCL2	Follicular Lymphoma	

MEMBERS :

Males:

-Leader : فيصل الطحان

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محمد باحاذق

أحمد الراشد

عبدالله بالعبيد

عبدالله السرجاني

أحمد الحربي

أنس السيف

داود إسماعيل

خالد الدوسري

فهد الفايز

محمد بن معيوف

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معاذ العبد الغني

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سيف المشاري

تميم الوهيبي

أحمد الرخيمي

رشيد البلاع

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محمد الأصقه

فايز الدرسوني

يزيد الدوسري

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-روان الحربي العتيبي

-وفاء الشنيفي

-الجوهرة

-رزان الزهراني

-رهف الشمري

-روان مشعل المسعد

-منيره

-لميس السويلم

-نوف العتيبي

-رزان الزهراني

-هديل عورتاني

-فاطمة بالشرف

-ابتسام المطيري

-رناد الفرم

-غرام جليدان

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-نورة القاضي

-آلاء الصويغ

-ريم القحطاني

-نورة بن حسن

Kindly contact us if you have any questions/comments and suggestions:

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GOOD LUCK! ☺

Resources:-

1- Females slides
2- Robbins reference book

Pathology

teamwork437