Neoplasia

Pathology team 434

Definitions: Blue.
Examples: Green.
Important: Red.
Extra explanation: Gray. . It is only there to help you understand. If you feel that it didn't add anything to you just skip it.
Diseases names: Underline.

Objectives

The student should:

A. Be able to define a neoplasm and knows the differences between benign and malignant neoplasms.

B. Understands the concepts governing the classification of tumors and their nomenclature.

C. Have a basic knowledge of the carcinogenic agents in human tumors including chemical, physical, viral, genetic and hormonal.

D. Understands important modes of tumors spread with common examples including spread. of carcinomas and sarcomas.

E. Be aware of the major clinical effects and features of tumors' including obstruction, ulceration, infection, anemia, cachexia and effects of products of tumors' including inappropriate hormone production.

F. Understands the basic of grading and staging of malignant neoplasms with special emphasis on the TNM staging system.

G. Know the role of tumors markers in the diagnosis and prediction of malign,. tumours prognosis.

Introduction To Neoplasm

Neoplasia, What is Cancer? Introduction to Neoplasm.

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[1] with that of normal tissues, which still persist in the same excessive manner even after the cessation[2] of the stimulus which evoked[3] the change.

- Different from **hyperplasia**, **metaplasia** and **dysplasia**.

- **Neoplasm** = **tumor**
- **Tumor** = **swelling** (in the clinical settings, tumor is usually used interchangeably with neoplasia)
- The study of tumors = **Oncology**. (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 of function in the accelerators, and loss of function in the breaks.
Imagine you have this car with a stuck accelerator, and the brakes are not working… This crazy car resembles a cancer cell.

Hallmarks of Cancer:

(1) self-sufficiency in growth signals whereby the growth of cancers becomes autonomous and is unregulated by physiologic signals. Neoplastic cells find ways to have their own signalling molecules or growth factors.
(2) lack of response to growth inhibitory signals that control non-neoplastic cellular proliferations such as hyperplasias. When the body sends signals to stop the cell proliferation, the cell doesn't respond.
(3) evasion[4] of cell death, allowing cancer cells to survive under conditions that induce apoptosis in normal cells. Normally, cells which have damaged DNA undergo apoptosis if they can't fix this damage; however, neoplastic cells find a way to evade, or run away from apoptosis.
(4) limitless replicative potential, thus making cancer cells immortal. Most cells in our bodies would only replicate for a number of times and then they will stop; cancer cells don't stop, but instead they keep going.

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[1] غير متناسق
[2] توقف
[3] أثار أو أحدث
[4] تجنب

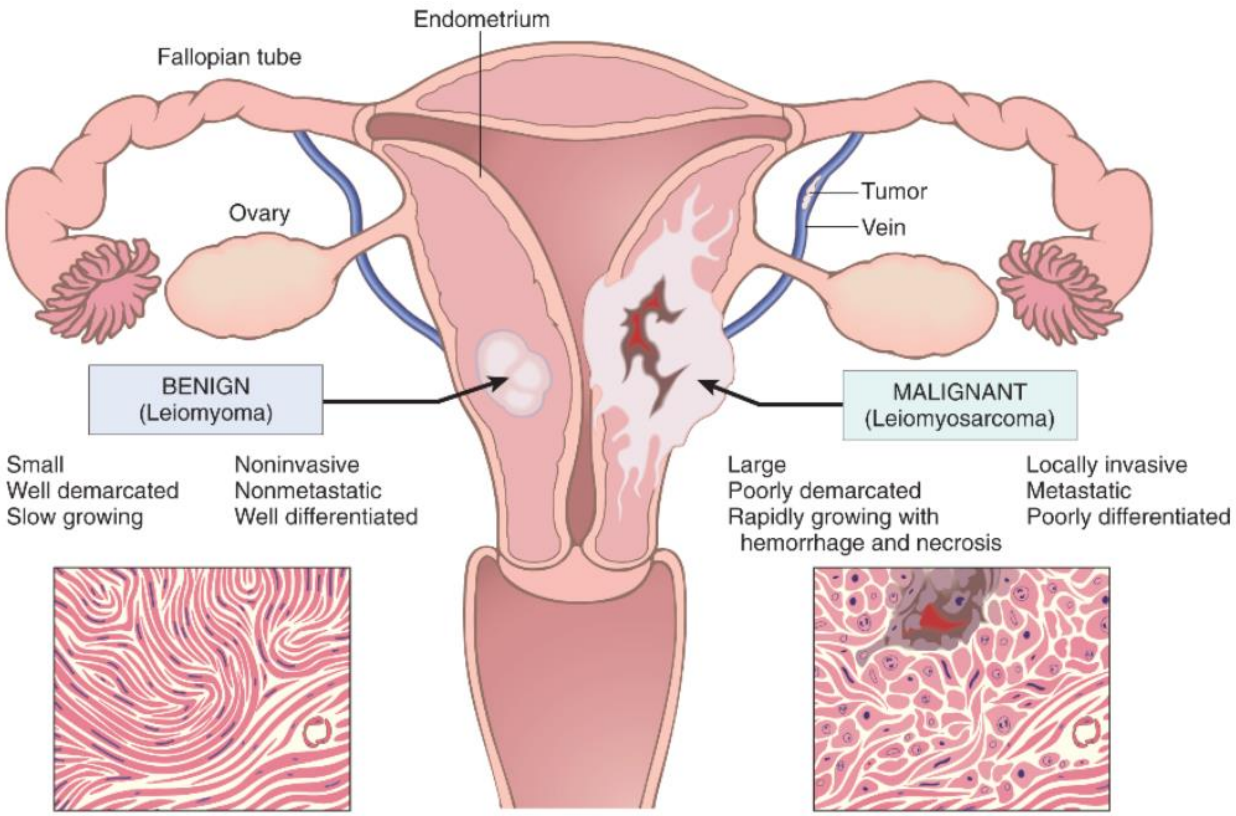
(5) development of **angiogenesis**[5] to sustain the growth of cancer cells. Neoplastic cells release substances that make the capillaries move to their direction. This gives it more nutrition.
(6) ability to **invade local tissues** and **spread** to distant sites; also called metastasis.
(7) **reprogramming of metabolic pathways**—specifically, a switch to aerobic glycolysis even when there is abundant oxygen.
(8) ability to **evade the immune system**. When cancer cells are mutated, they start producing weird proteins that other cells of the body don't produce. Normally, the immune system should get ridd of this cell but cancer cells find a way to evade the immune system.

[5] الأوعية الدموية

Neoplasia Classification

Benign[6]	Malignant[7]
Cannot spread to distant sites	Can spread to distant sites
Patient generally survives	Causes death - if not treated
Will remain localized	Can invade and destroy adjacent structures

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



All tumors have two basic components:

1. **Parenchyma:** made up of **neoplastic cells.**
2. **Stroma:** made up of **non-neoplastic**, **host-derived** **connective tissue** and **blood vessels.**

[6] حميد
[7] خبيث

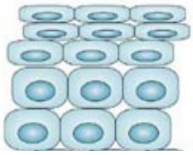
The parenchyma:

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

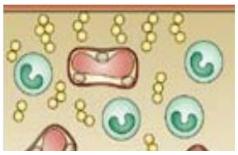
The stroma:

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

1. Proliferative neoplastic parenchyma



2. Supportive fibrovascular stroma



Nomenclature of Benign and Malignant Neoplasm

Nomenclature of benign and malignant cancers, How to name cancers, mixed tumors explained

1. **Benign tumors.**
2. **Malignant tumors.**
3. **Mixed tumors.**

Benign Tumors

- Type of cell (prefix)+ **-oma** (suffix)

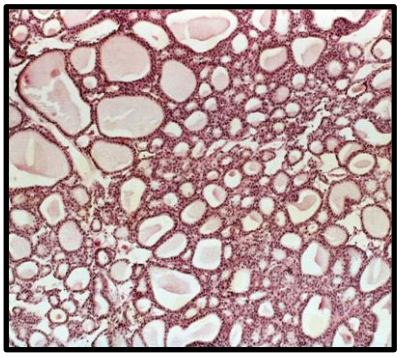
Examples:

- **Benign tumor arising in fibrous tissue:** Fibro + oma = **Fibroma**
- **Benign tumor arising in fatty tissue:** Lipo + oma = **lipoma**
- **Benign tumor arising in cartilage:** chondro + oma = **chondroma**
- **Benign tumor arising in skeletal muscle:** Rhabdomyo + oma = **rhabdomyoma**
- **Benign tumor arising in smooth muscle:** Leiomyo + oma = **leiomyoma**

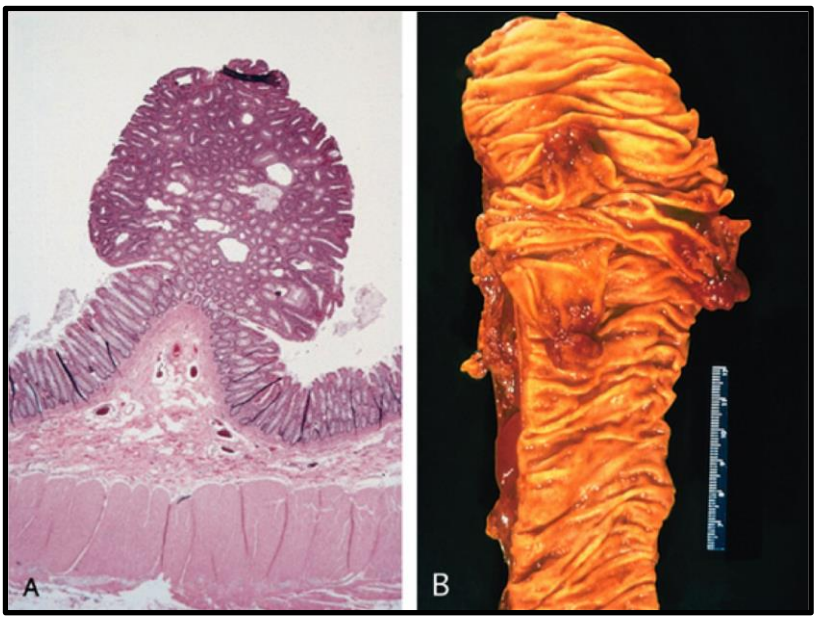
Exception for (epithelial benign tumors). They are classified on the basis of :

- The cell of origin.
- Microscopic pattern.
- Macroscopic pattern.

1. **Adenoma:** (adeno = gland) benign epithelial neoplasms
   a) producing a glandular pattern..
   b) **OR** derived from glands (not necessarily producing glandular structures).

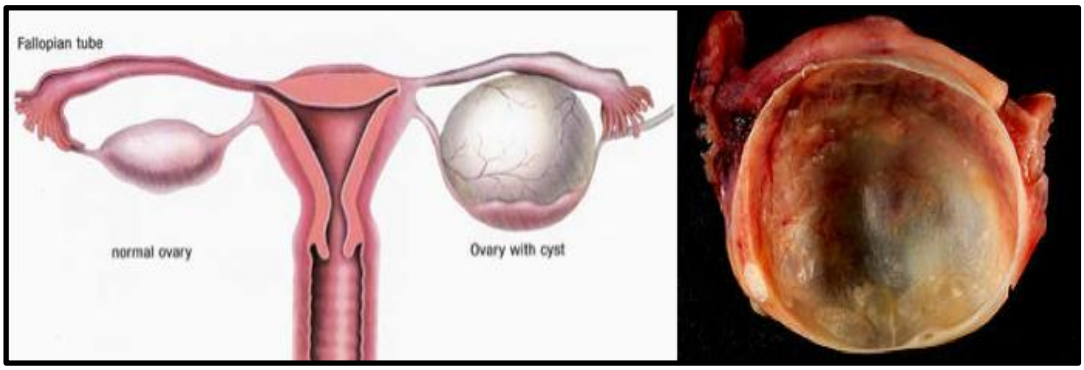


2. **Papilloma:** benign epithelial neoplasms growing on any surface that produces a microscopic or macroscopic **finger-like pattern.**
   - **Polyp:** a mass that projects above a mucosal surface forming a **macroscopically** visible structure.



A. Colonic polyp. **B.** Nasal polyp.

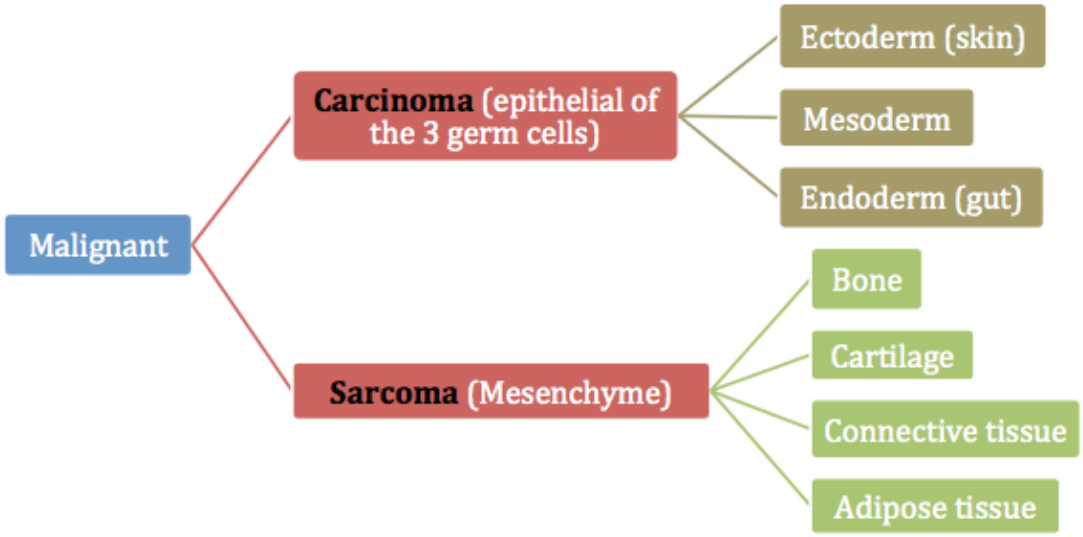
3. **Cystadenoma:** occurs in ovaries.



Examples of benign epithelial neoplasms:

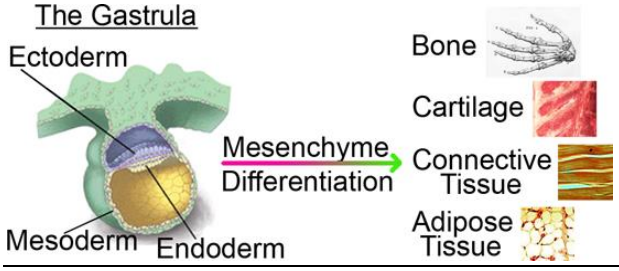
- **Respiratory airways:** Bronchial adenoma.
- **Renal epithelium:** Renal tubular adenoma.
- **Liver cell:** Liver cell adenoma.
- **Squamous epithelium:** squamous papilloma.

Malignant Tumor



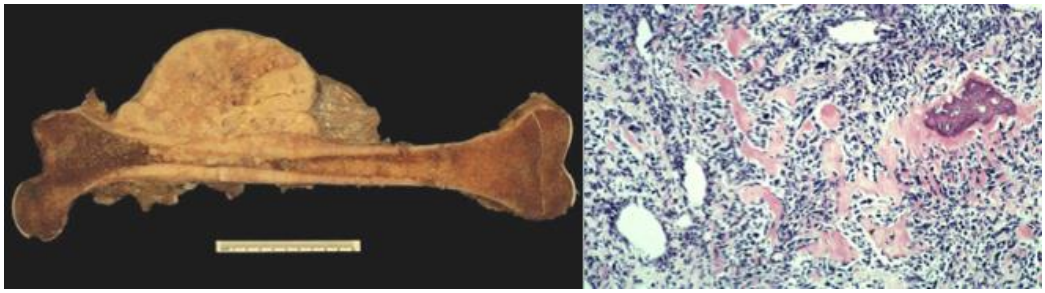
1. Malignant tumors arising from **epithelial origins**: **CARCINOMA**
2. Malignant tumor arising in **mesenchymal tissue**: **SARCOMA**

What's mesenchymal tissue?



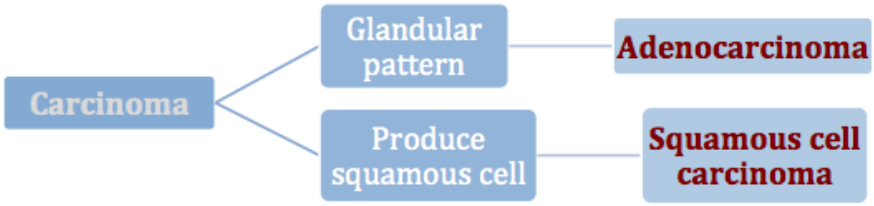
1] Sarcoma

- From fibrous tissue: **Fibrosarcoma**
- From bone: **Osteosarcoma**

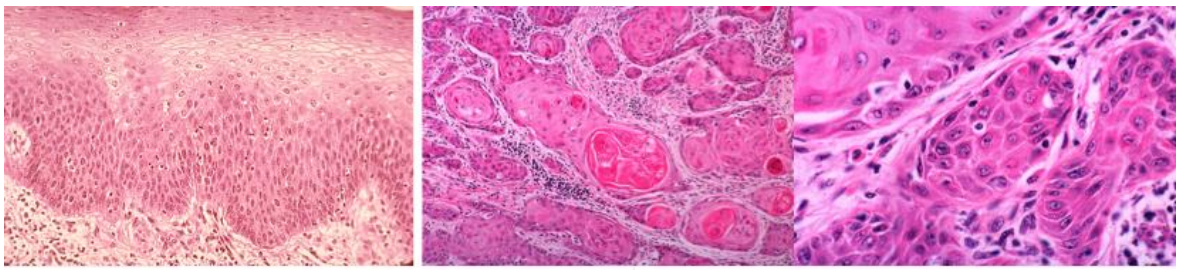


- From cartilage: **chondrosarcoma**

2] Carcinoma

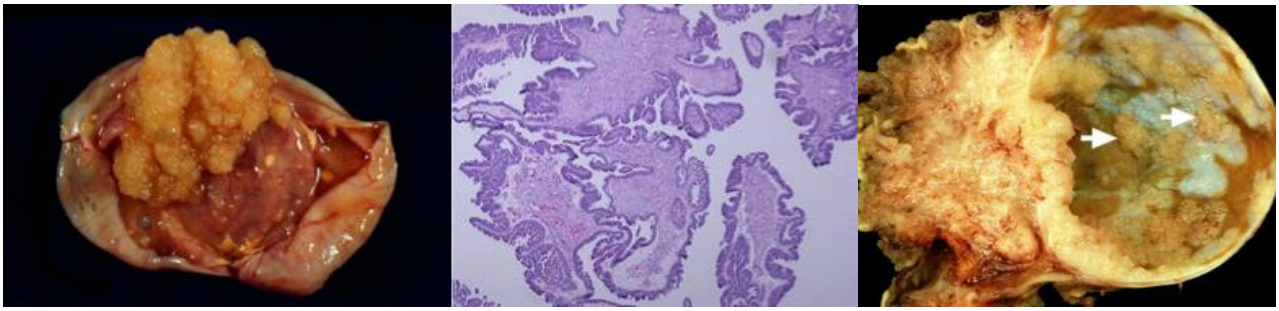


- **Squamous cell carcinoma.**
- **Renal cell adenocarcinoma.**
- **Cholangio**carcinoma[8].



Normal squamous epithelium Squamous cell carcinoma

Other descriptive terms may be added such:



Papillary Cystadenocarcinoma of the Ovary

Exceptions (should be memorized):

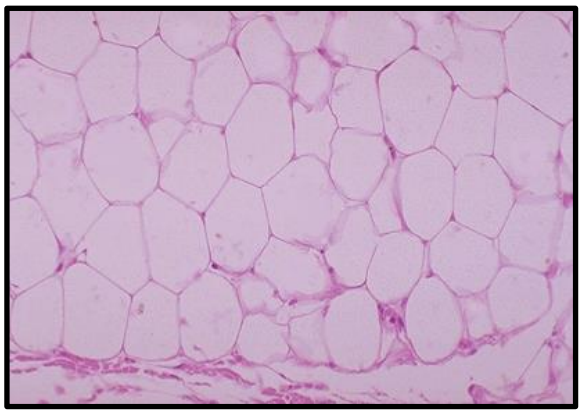
- **Melanoma** (skin)
- **Mesothelioma** (mesothelium)
- **Seminoma** (testis)
- **Lymphoma** (lymphoid tissue)

Nomenclature of benign and malignant neoplasm:

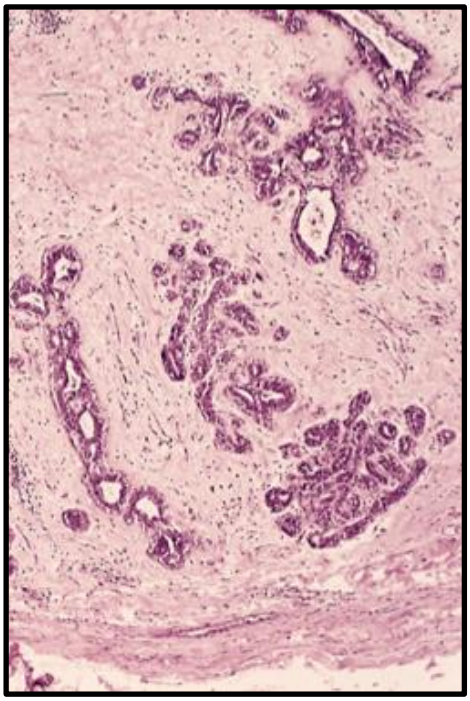
- Based on the **biological behavior**: **Benign** and **malignant.**
- Based on the cell of **origin**:
  - **One** neoplastic cell type: **lipoma**, **adenocarcinoma.**

[8] سرطان الأوعية الصفراوية

- **More than one** neoplastic cell type: **fibro**adenoma.
- **More than one neoplastic cell type** derived from **more than one germ-cell layer**: **teratoma.** (see next page).
- Derived from **embryonic tissue**: **blastoma** (could be **benign**: **osteoblastoma**, or **malignant**: **neuroblastoma**)



Lipoma



Fibroadenoma

Teratoma

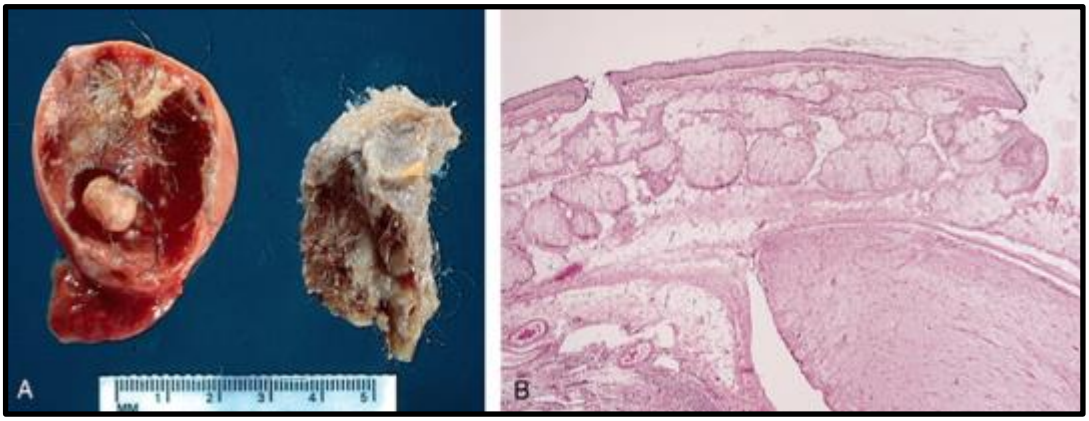
Teratoma: Teratoma contains recognizable **mature** or **immature** cells or tissues representative of more than **one germ-cell layer,** and sometimes **all three**.

- Teratomas originate from **totipotential cells**[9] such as those normally present in the **ovary** and **testis**.

Such cells have the capacity to differentiate into any of the cell types found in the adult body. So they may give rise to neoplasms that mimic[10] **bone**, **epithelium**, **muscle**, **fat**, **nerve** and other tissues.

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

- **Benign** → (**mature**) teratoma.
- **Malignant** → (**immature**) teratoma.



[9] an embryonic cell that is capable of developing into any variety of body cells.

[10] تحاكي

Hamartoma & Choristoma

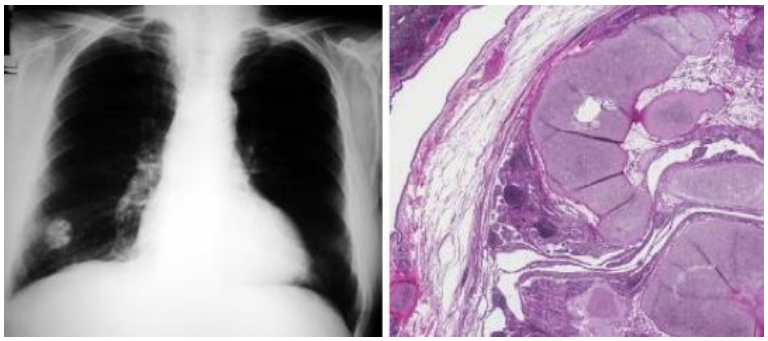
Hamartoma: a mass composed of cells **native to the organ**.

- **pulmonary 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.

Choristoma: a mass composed of normal cells in a **different location**.

- **pancreatic choristoma** in **liver** or **stomach**.
- **It is a malformation[11] and not neoplasm.**



Pulmonary Hamartoma

- They are distinguished from neoplasms by the fact that **they do not exhibit continued growth**.
- They are a group of **tumor-like tissue masses** which may be confused with neoplasms.

[11] تشوه

- Historic eponyms – "first described by…"

Hodgkin's disease	**Malignant lymphoma** (HL) of B Lymphocyte cell origin
Burkitt tumor	NHL – B Lymphocyte cell in **children** (jaw and GIT)
Ewing tumor	**Bone tumor:** Primitive neuroectodermal tumor (PNET)
Grawitz tumor	**Kidney tumor** - clear cell adenocarcinoma
Kaposi sarcoma	Malignant tumor derived from **vascular epithelium** (AIDS)
Brenner tumor	**Ovarian tumor** derived from **Brenner cells**
Merkel tumor	**Skin tumor** derived from Merkel cell

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

Characteristics of benign and malignant neoplasms

How to tell a benign and malignant tumor apart?

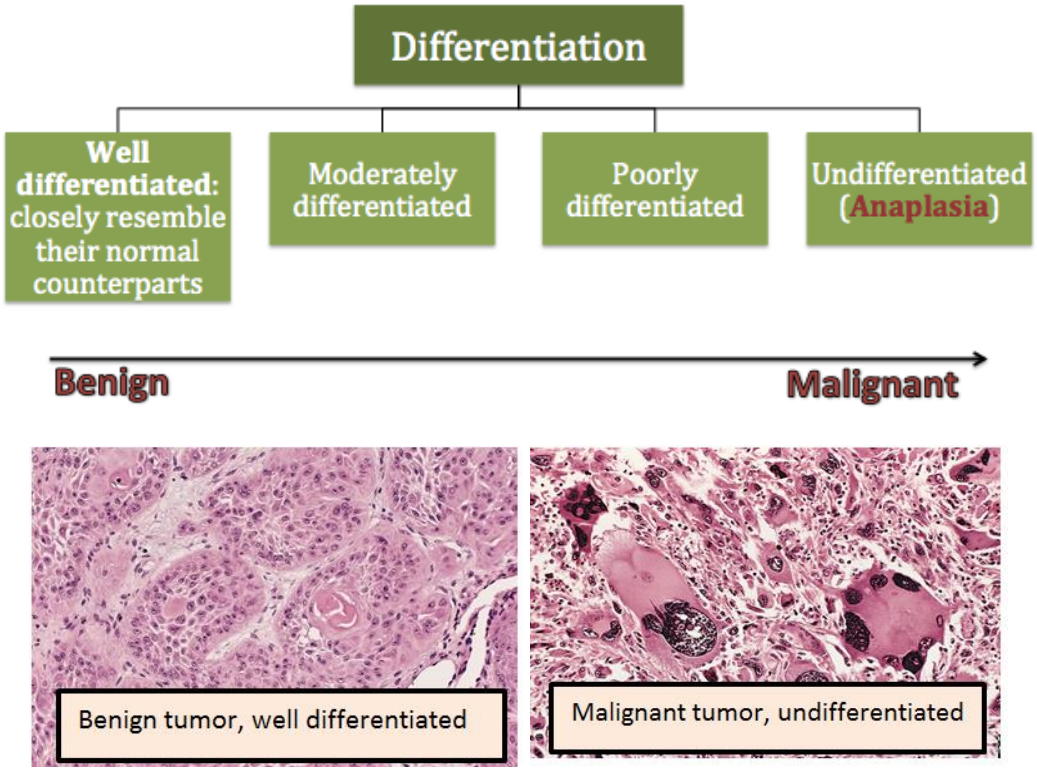
- Differentiation and anaplasia.
- Rate of growth.
- Local invasion.
- Metastasis (most important characteristic to determine malignancy)

Differentiation

Differentiation: the extent to which the **parenchymal cells** of the tumor resemble[12] their normal counterparts[13] **morphologically** and **functionally**.

1. **Well differentiated** → **benign** (mature) teratoma.
2. **Undifferentiated** → **malignant** (immature) teratoma.

Well differentiated means that the cell looks like other normal cells in the tissue. As a consequence, it usually still have the same function.



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[12] تشابه
[13] نظائرهم

Rate of Growth

1- Benign :

1. Grows slowly.
2. are affected by blood supply, hormonal effects, and location.

2- Malignant:

1. grows faster.
2. correlated with the level of differentiation.

Local Invasion

1- Benign :

1. Remain localized.
2. cannot invade.
3. usually encapsulated

2- Malignant:

1. Destruction.
2. progressive invasion
3. Usually not encapsulated

Metastasis

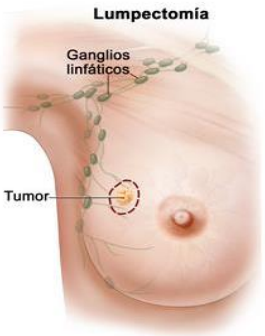
Metastasis[14]: The development of secondary implants discontinuous with the primary tumor, possibly in remote tissues.

Approximately 30% of patients present with clinically evident metastases.

Generally, the larger the primary tumor and the more it is anaplastic, the more likely it is metastasized.

It has three pathways :

1- lymphatic spread:



- favored by *carcinoma* (Malignant epithelium).

1. Breast carcinoma : metastasis to axillary lymph nodes.
2. lung carcinoma : metastasis to bronchial lymph nodes.

2- Hematogenous spread:

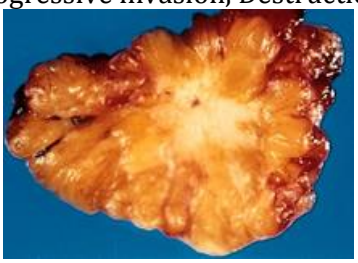
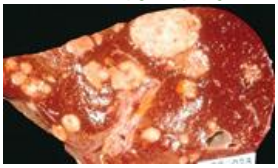
- favored by *sarcomas* and are also used by carcinomas.
- Veins are commonly invaded. (because they are thinner than arteries)
- most frequently involved secondary sites:

1. the two L's : lungs and liver. The liver is the usual location because all malignancies in the GIT can be metastasized through the portal vein.
2. the two B's : bone and breast.

3- Body cavities:

1. Pleural.
2. Peritoneal cavities.
3. cerebral ventricles.

[14] قدرة الورم على الانتشار

	Benign tumors	Malignant tumors
Differentiation and anaplasia	well differentiated	some are well differentiated and some are anaplastic (poorly differentiated)
Rate of growth	Grows slowly	Grows faster
Local invasion	Remains localized , does not invade. 	Progressive invasion, Destruction. 
Metastasis	there is no metastasis	there is metastasis Ex: انتقال سرطان القلون للكبد أيضا 

SUMMARY

Characteristics of Benign and Malignant Tumors

- Benign and malignant tumors can be distinguished from one another based on the degree of differentiation, rate of growth, local invasiveness, and distant spread.
- Benign tumors resemble the tissue of origin and are well differentiated; malignant tumors are poorly or completely undifferentiated (anaplastic).
- Benign tumors are slow-growing, whereas malignant tumors generally grow faster.
- Benign tumors are well circumscribed and have a capsule; malignant tumors are poorly circumscribed and invade the surrounding normal tissues.
- Benign tumors remain localized to the site of origin, whereas malignant tumors are locally invasive and metastasize to distant sites.

Dysplasia

Dysplasia: a loss in the uniformity[15] of the individual cells and a loss in their **architectural orientation** (not cancer but precancer).

- **What is the main difference between dysplasia and cancer?**

1. **Dysplastic cells don't** invade the **basement membrane** while **cancer cells do**.
2. Dysplasia is reversible, but cancer is irreversible.

Characteristics:

1. Non-neoplastic.
2. Occurs mainly in the epithelial cells.
3. Dysplastic cells show a degree of : pleomorphism (تعدد الشكل), hyperchromasia, increased mitosis and loss of polarity.
4. might be reversible.
5. If dysplastic changes involve the **entire thickness of the epithelium** it is called **CARCINOMA IN-SITU** = severe dysplasia

Carcinoma in-situ: an intraepithelial malignancy in which malignant cells involve the entire thickness of the epithelium without penetration of the basement membrane.

- Applicable only to epithelial neoplasms.

Dysplasia features:

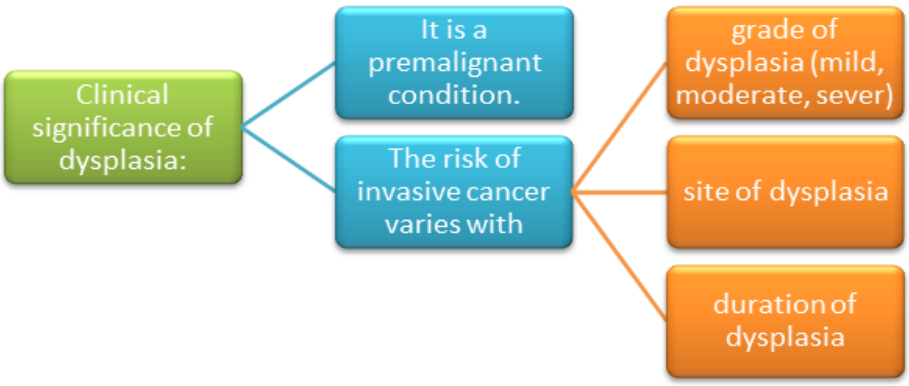
- Cytoplasmic abnormalities due to failure of normal maturation
- Increased rate of multiplication.
- Disordered maturation.
- Nuclear abnormality
  - Increased N/C ratio[16].
  - Irregular nuclear membrane.
  - Increased chromatin content.

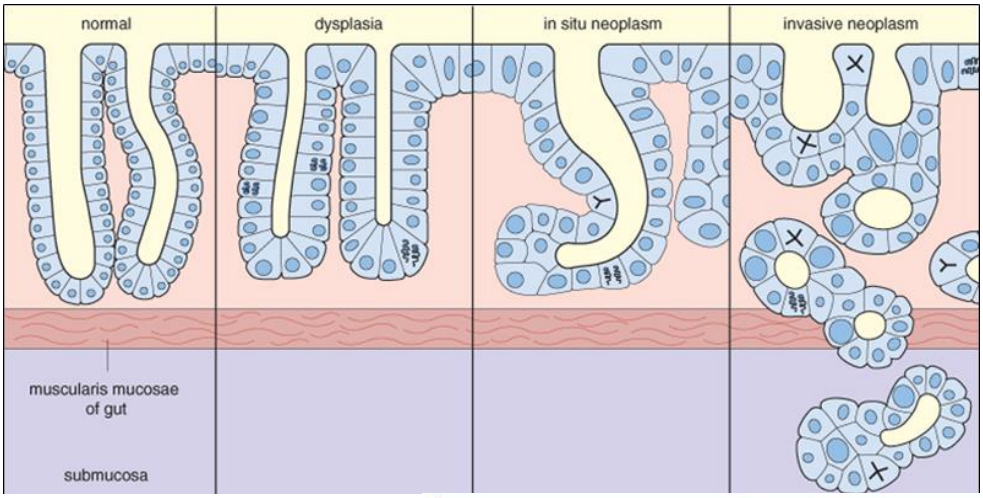
Differences between dysplasia and cancer.

- lack of invasiveness.
- Reversibility.

[15] انتظام

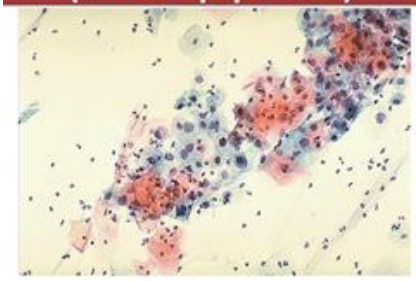
[16] بمعنى أن النواة يكبر حجمها بالنسبة للخلية.. فالنواة حجمها الطبيعي بالنسبة للخلية هو ٦\١١ أو ٤\١١ .. ولكن في حالة الديسبلازيا يكون حجم النواة مقارب لحجم الخلية.. تقريبا ١\١١.

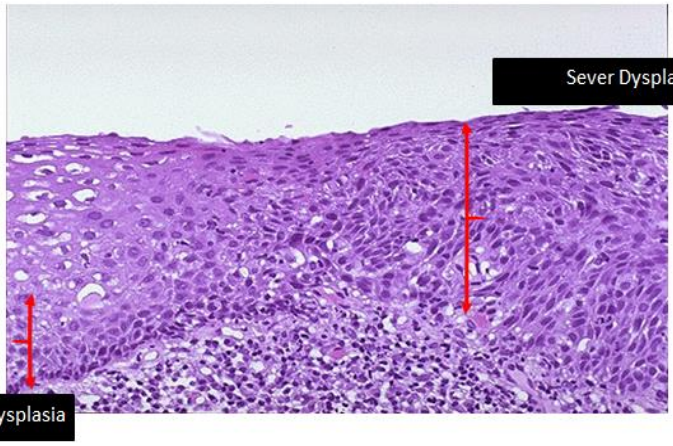




Dysplasia
Uterine cervix

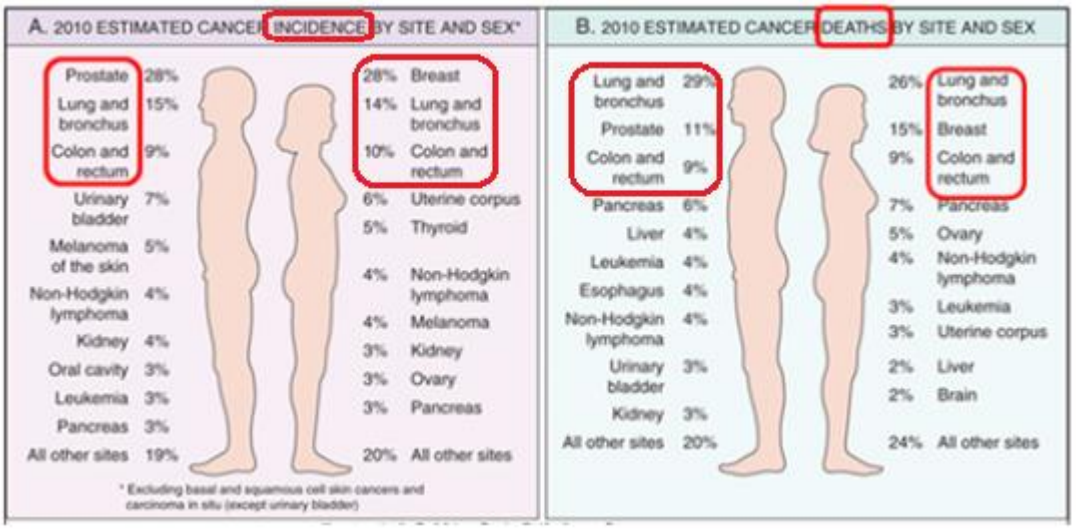
Dysplasia
(cervical pap smear)



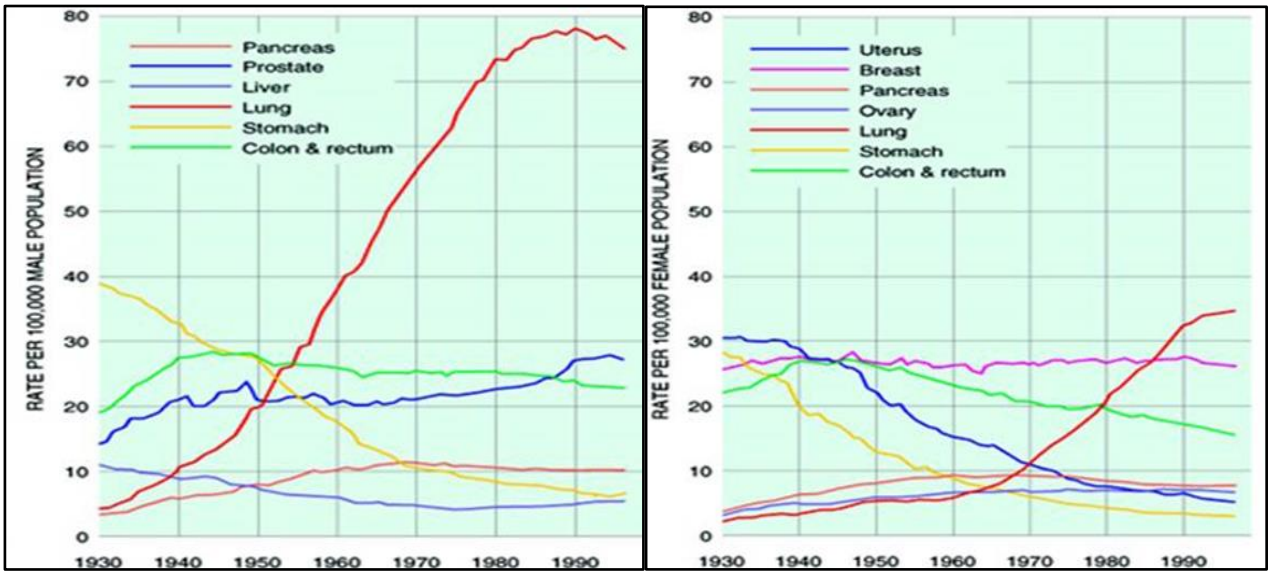


Epidemiology of Neoplasia

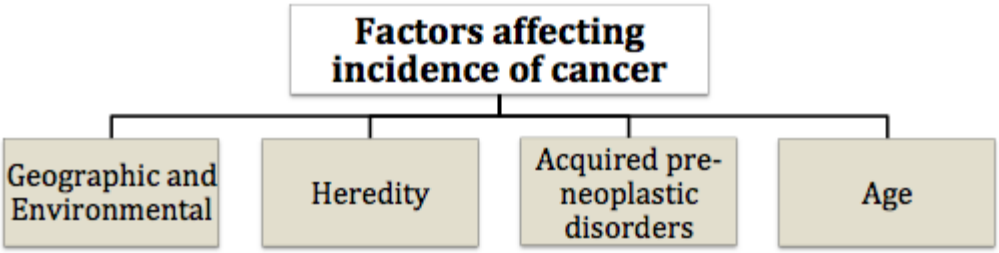
1. Will help to discover etiology (reason).
2. Planning of preventive measures.
3. To know what type of cancer is common and what is rare.
4. Development of screening methods for early diagnosis**.**



- **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.



Geographic and Environmental

- Rate of stomach carcinoma in Japan is seven times the rate in North America and Europe.
- Breast carcinoma is five times higher in North America comparing to Japan.
- Liver cell carcinoma is more common in African populations.

- Asbestos → **mesothelioma**
- Smoking → **lung cancer**
- Multiple sexual partners → **cervical cancer**
- Fatty diets → **colonic cancer**

Age

- Generally, the frequency of cancer increases with age.
- Most cancer mortality occurs between 55 and 75.
- Cancer mortality is also increased during childhood
- Most common tumors of children: Leukemia, tumors of CNS, Lymphomas, soft tissue and bone sarcomas.

Hereditary

1. **Autosomal dominant cancer syndromes: Inheritance** of a single mutant gene greatly increases the risk of developing neoplasm.

E.g. Retinoblastoma in children (it is very rare but is certain families it will be 10000 times more common because they inherit an abnormal gene from the parents)

- 40% of Retinoblastomas are familial.

Examples of Autosomal Dominant Cancer Syndromes:

Gene	Inherited Predisposition
RB	Retinoblastoma
TP53	Li-Fraumeni syndrome (various tumors)
p16INK4A	Melanoma
APC	Familial adenomatous polyposis/colon cancer
BRCA1, BRCA2	Breast and ovarian tumors
MEN1, RET	Multiple endocrine neoplasia 1 and 2

2. Autosomal Recessive Syndromes of Defective DNA Repair :

•Small group of autosomal recessive disorders

•Characterized by DNA instability

•E.g. **xeroderma pigmentosum** (cancer related to sun exposure)

3. Familial Cancers of Uncertain Inheritance:

- All common types of cancers occur in familial form E.g. breast, colon, ovary, brain

- **unique features of familial cancer :**
  1. Start at **early age**
  2. Multiple or bilateral[17]
  3. Two or more relatives are known to have some type of cancer

Acquired pre-neoplastic disorders:

Some Clinical conditions that predispose to cancer:

1. Dysplastic bronchial mucosa in smokers → lung carcinoma
2. Liver cirrhosis[18] → liver cell carcinoma
3. Margins of chronic skin fistula → Squamous cell carcinoma

[17] Cancer that occurs in both of a pair of organs, such as both breasts, ovaries, eyes, lungs, kidneys, or adrenal glands, at the same time.

[18] تليف الكبد

SUMMARY

Epidemiology of Cancer

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

ETIOLOGY OF CANCER: CARCINOGENIC AGENTS

Carcinogenic Agents:

- ❏ Chemicals.
- ❏ Radiation.
- ❏ Microbial agents. (infectious agents including viruses and microbes)

1- Chemical Carcinogens

- Natural or synthetic. (the only thing they have in common is that they lead to cancer)
- Direct reacting or indirect. (Come to the body and causes cancer directly) Indirect → need metabolic conversion to be active and carcinogenic. (They're not carcinogenic but when they come to the body, the body makes enzymatic changes that will lead to cancerous metabolites)

- Indirect chemicals are called " **procarcinogens** " and their active end products are called "**ultimate carcinogens**". (**Procarcinogens** → metabolism and breakdown → **ultimate carcinogens**)
- All direct reacting and ultimate chemical carcinogens are highly reactive as they have **electron-deficient atoms.** (Free radical)
- They react with the electron rich atoms in **RNA**, **DNA** and other **cellular proteins.**

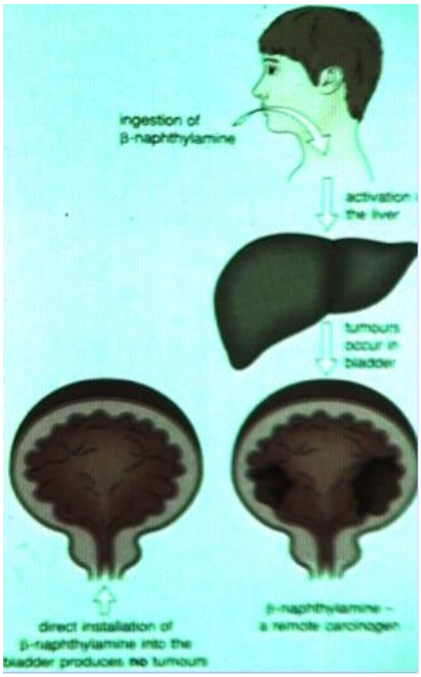
Alkylating agents.

- (**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.

Polycyclic hydrocarbons: (Indirectly active)

1. Cigarette smoking.
2. Animal fats during broiling meats. (some of the meats' hydrocarbon will be converted to aromatic hydrocarbon)
3. Smoked meats and fish. (have aromatic and cyclo hydrocarbon like benezeprene)

Aromatic amines and azo dyes:



- **B-naphthylamine**

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.

- causes **bladder cancer,** it is used in **rubber industries** and **aniline dye**.
- Some azo dyes are used to color food also can cause bladder cancer.

Other substances:

- **Nitrosamides** and **nitrosamines** are used as preservatives[19]. They may cause **gastric cancer.**
- **Aflatoxin B**: produced by ***Aspergillus***[20] growing on improperly stored grains. It cause hepatocellular carcinoma. (In the liver)

Mechanism of action of chemical carcinogens:

- Most of them are **mutagenic** (cause mutations to genes).
- **RAS** and **P53** are common targets.

2- Radiation Carcinogenesis:

- UV rays of sunlight. **(Skin cancer)**
- X-rays. **(leukemia and cancer)**
- Nuclear radiation (in wars). **(leukemia, lung colon and thyroid cancer.)**
- Therapeutic irradiations[21]. (They use it to treat tumors, but could also cause them)

Radiation has mutagenic effects: **chromosomes breakage**, **translocations**, and **point mutations**.

UV rays of sunlight :

- Can cause skin cancers: melanoma, squamous cell carcinoma, and basal cell carcinoma.
- It is capable of damaging DNA.
- With extensive exposure to sunlight, the repair system is overwhelmed[22] → skin cancer.
- They cause mutations in **P53** gene.

---

[19] مواد حافظة
[20] نوع من الفطريات
[21] الإشعاع العلاجي
[22] لم يعد قادر على العمل

3- **Viral Carcinogenesis:**

(هو جماد بمجرد ما يدخل الجسم يبدا ضرره)

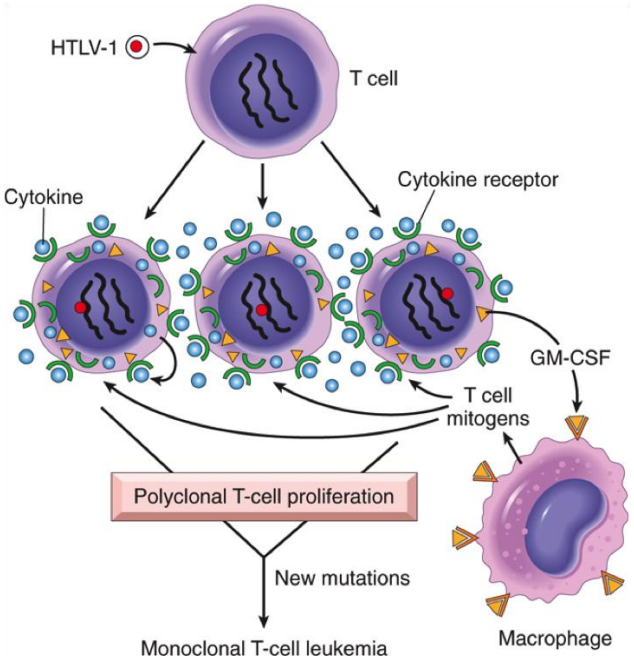
- **Viral and Microbial oncogenesis:**
  - DNA viruses.
  - RNA viruses.
  - other organisms.

- carry genes that **induce cell replication** as part of the **viral life cycle**.
- host cell has **endogenous genes** that maintain the **normal cell-cycle.**
- Viral infection **mimics** or **blocks** these normal cellular signals necessary for growth regulation.

RNA Oncogenic viruses:

Human T-Cell Leukemia Virus type 1 (HTLV-1).

- **RNA retrovirus** targets / transforms T-cells.
- Causes **T-Cell leukemia** , **Lymphoma**.
- Endemic in **Japan** and **Caribbean**.
- Transmitted like HIV ***but*** only **1%** of infected develop T-Cell leukemia/Lymphoma.
- **20-30 year** latent period (the patient could carry the virus for 20-30 years)
- **No cure or vaccine.**
- Treatment: **chemotherapy** with common relapse.



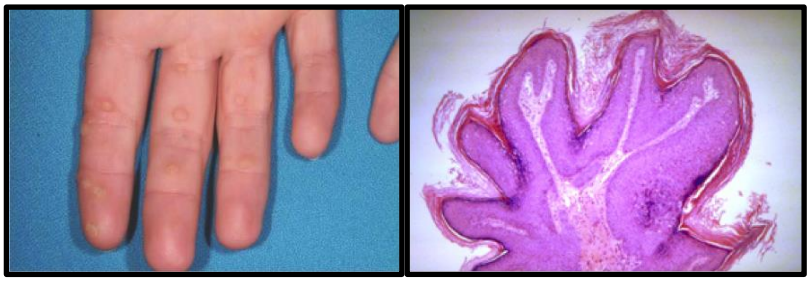
DNA Oncogenic Viruses:

- virus DNA forms stable association with host's DNA. (Lead to neoplastic cells)
- transcribed viral DNA transforms host cell

Examples:

1. Human papillomaviruses (HPV).
2. Epstein-Barr (EBV).
3. Hepatitis B (HBV).
4. Kaposi sarcoma herpesvirus. (mostly found in aids patients)

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.
- **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.**

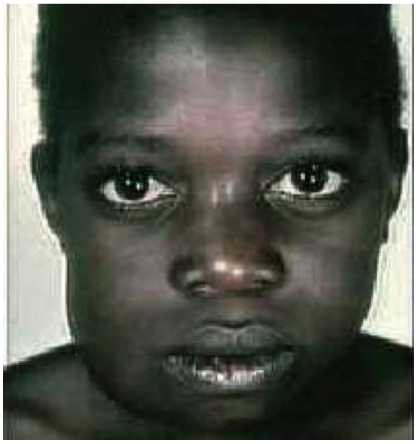
EBV infection may cause malignancy:

- **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**.

- ❖ **Burkitt Lymphoma:**



  - 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 Pylori[23]**:** Rarely leads to cancer.

- bacteria infecting the stomach.
- Implicated in **peptic ulcers.**
  - **gastric lymphoma.**
  - **Mucosal Associated Lymphoid Tumor (MALT).**
  - **gastric carcinoma.**

[23] جرثومة المعدة

CARCINOGENESIS

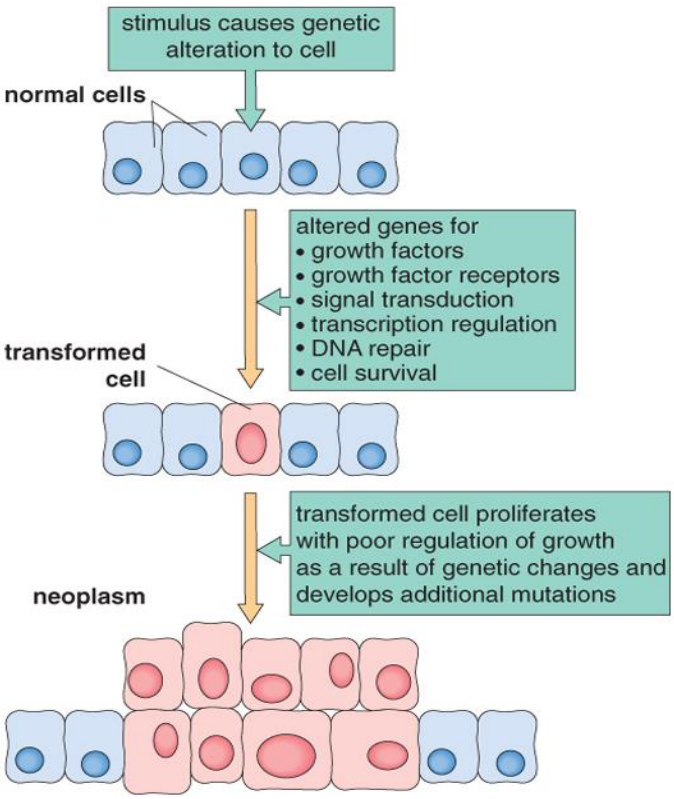
This is a video from our team that goes through the normal cell cycle. It helps in understanding the genes, their functions, and what goes wrong during neoplastic changes:
http://www.youtube.com/watch?v=Y2h3XJ-f_2s&feature=youtu.be

Carcinogenesis: is a multistep process at the phenotypic,, and genetic level of the neoplasm.

It starts with damage in the genetic material:

- Environmental
- Chemical
- Radiation
- Viral
- 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.



Where are the targets of the genetic damage ?

FOUR regulatory genes are the main targets:

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.

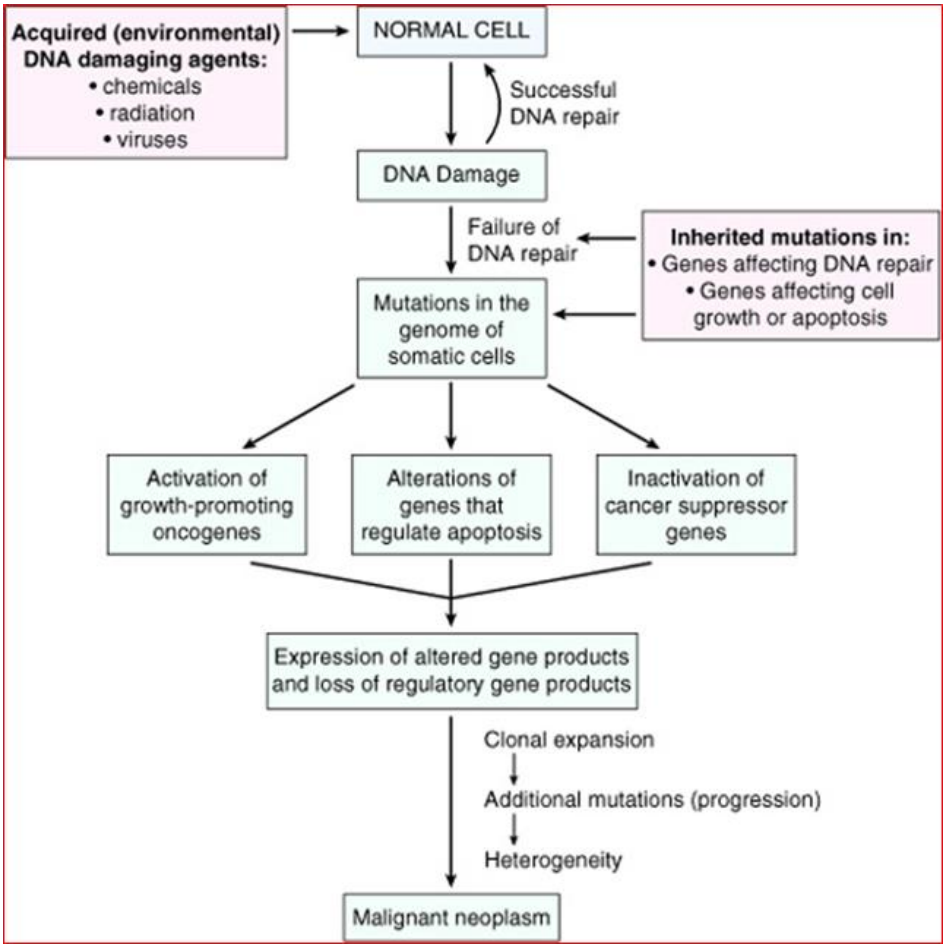
   Proto-oncogene → mutation → oncogene

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.

3) Genes regulating **apoptosis**.
4) **DNA repair** genes.



The student that doesn't understand why these are targets for carcinogens should take a 1.5 minute break and come back to read the following mini section:

What is the real problem with cancer cells? They grow uncontrollably. Why? because their protooncogenes (accelerators) and over functioning, or because of their tumor suppressor genes (breaks) are not working. So, if I am a carcinogen and I want to cause cancer in a cell I would mutate the proto-oncogenes and make them stronger and over functioning. Or I could mutate the tumor suppressor genes and make them weaker and less functioning.

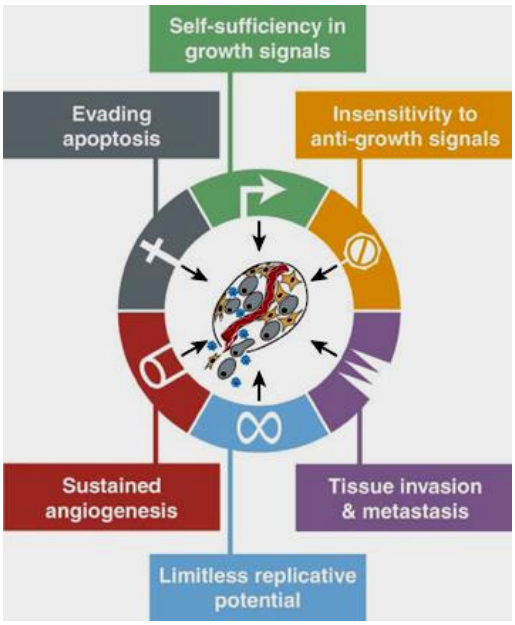
Why would I target genes regulating apoptosis? Because normally, when a cell's DNA is damaged a lot, and the cell can't fix it, the apoptosis pathway is turned on and the cell suicides. The cell says: " My DNA is so messed up I should suicide because I might harm my friend (which is you) "

Neoplastic cells turn off the apoptosis pathway making the cell have many damages at the DNA which might finally lead to malignancy.

End of mini section. Thank you.

Main changes in cell physiology that leads to the formation of a malignant phenotype:

- Self-sufficiency[24] in growth signals.
- Insensitivity to growth-inhibitory signals.
- Evasion[25] of apoptosis.
- Limitless replicative potential.
- Sustained angiogenesis.
- Ability to invade and **metastasize**.



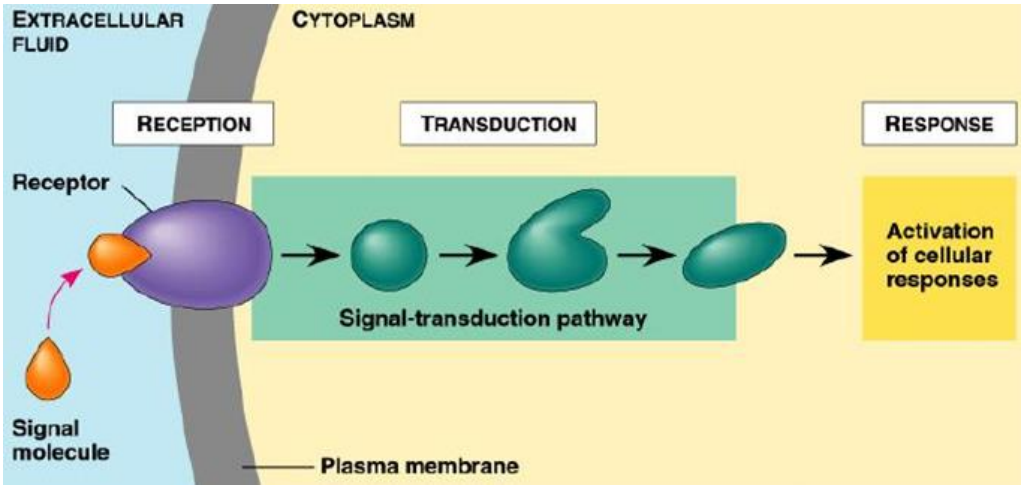
[24] الاكتفاء الذاتي
[25] تجنب

Self-sufficiency in Growth signals

- **Oncogene**: Gene that promote autonomous[26] cell growth in cancer cells
- They are derived by mutations in **proto-oncogenes**.
- They are characterized by the ability to promote cell growth in the absence of normal growth-promoting signals.
- **Oncoproteins**: are the products.

Remember the cell cycle!

Binding of a **growth factor** to its **receptor** on the cell membrane → Activation of the growth factor receptor leading to **activation of signal-transducing proteins** → Transmission of the signal to the **nucleus** → Induction[27] of the DNA transcription → Entry in the cell cycle and cell division



HOW CANCER CELLS ACQUIRE SELF-SUFFICIENCY IN GROWTH SIGNALS ?

1- Growth factors:

Cancer cells are capable to synthesize the same growth factors to which they are responsive.

- **Sarcomas** → **TGF-a** (transforming growth factor)
- **Glioblastoma**[28] → **PDGF**

Platelet-derived growth factor (PDGF) is 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.

---

[26] مستقل

[27] إحداث / بدء

[28] 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:

1. Receptors → **mutation** → continuous signals to cells and uncontrolled growth.
2. Receptors → **overexpression** → cells become very sensitive → hyperresponsive to normal levels of growth factors.

For example when number of receptors of growth hormone increase in cell surface they stimulate more cell division.

Epidermal Growth Factor (EGF) Receptor family:

- **HER2:** is a member of the epidermal growth factor receptor (EGFR/ERBB) family.

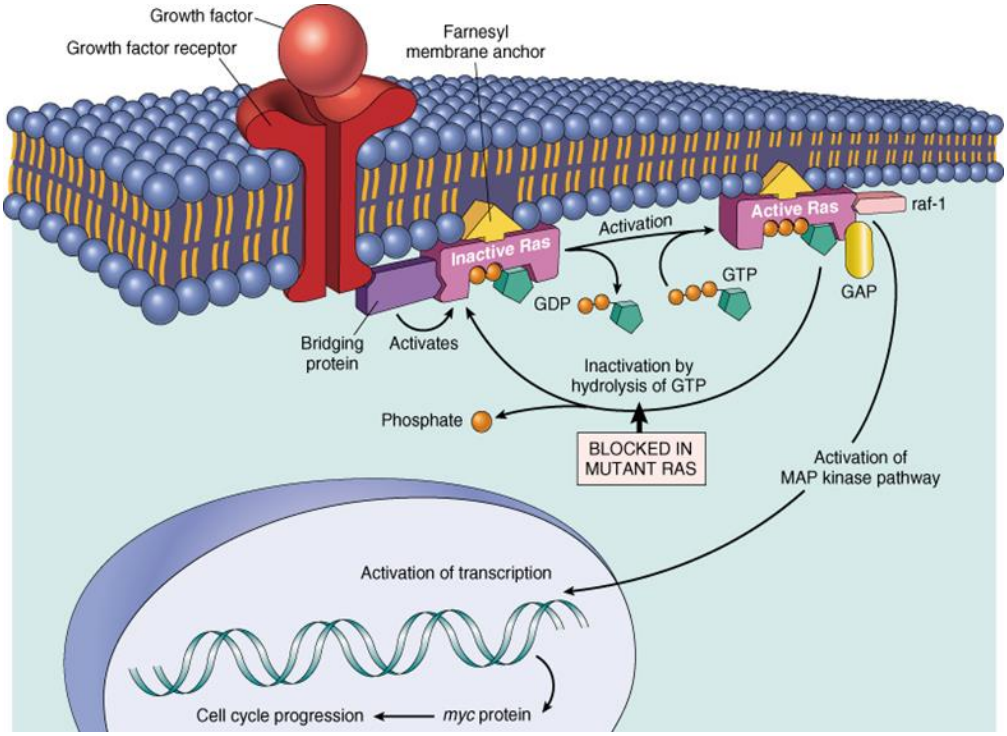
    - Amplified in breast cancers and other tumors.
    - **High levels** of HER2 in **breast cancer** indicate **poor prognosis**.
    - **Anti- HER2 antibodies** are used in treatment.

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

They receive signals from activated growth factors receptors and transmit them to the nucleus.

RAS: Ras protein family members are involved in transmitting signals within cells (cellular signal transduction).

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



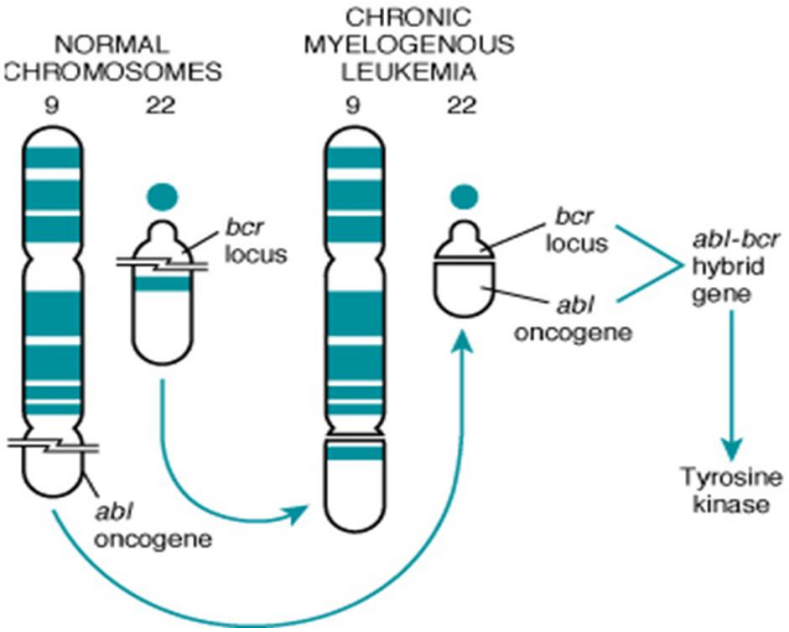
ABL gene:

- APL **proto-oncogene** has a **tyrosine kinase**[29] activity
- Its activity is controlled by **negative regulatory mechanism.**

In **chronic myeloid leukemia** (**CML**): Chronic myelogenous leukemia (CML) is a cancer that starts inside bone marrow. This is the soft tissue in the center of bones that helps to form all blood cells. CML causes an uncontrolled growth of immature cells that make a certain type of white blood cell called **myeloid cells**.

- **t (9,22)** → 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**[30]) which is inhibitor of ABL kinase.



4- Nuclear transcription factors:

Mutations may affect genes that regulate transcription of DNA → growth autonomy.

- **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 the cell cycle begins, but in tumors there is **sustained expression of MYC** → continuous proliferation.

- **Burkitt Lymphoma**[31]: MYC is dysregulated due to **t(8,14)**

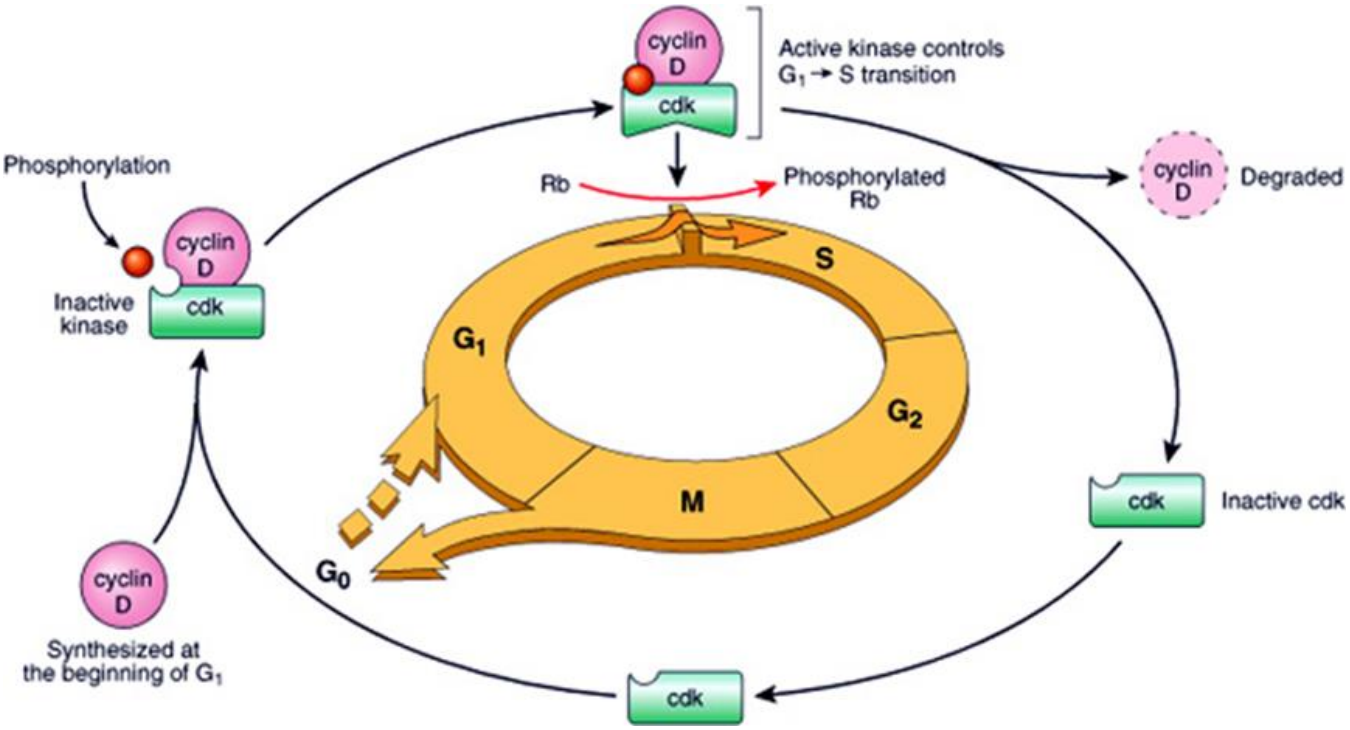
[29] A **tyrosine kinase** is an enzyme that can transfer a phosphate group from ATP to a protein in a cell.
[30] cancer drug

5- Cyclins and cyclin-dependent kinases (CDKs)

Cyclin-dependent kinases/cyclin

- Progression[32] of cells through cell cycles is regulated by **CDKs** after they are activated by binding with **cyclins**.
- Gain of function mutations that affect cyclins and CDKs will lead to **cell proliferation**.

- **Cyclin D** genes are overexpressed in **breast**, **esophagus** and **liver** cancers.
- **CDK4** is amplified in **melanoma** and **sarcomas**.



[31] Burkitt lymphoma is a very fast growing form of non-Hodgkin's lymphoma.

[32] تقدم

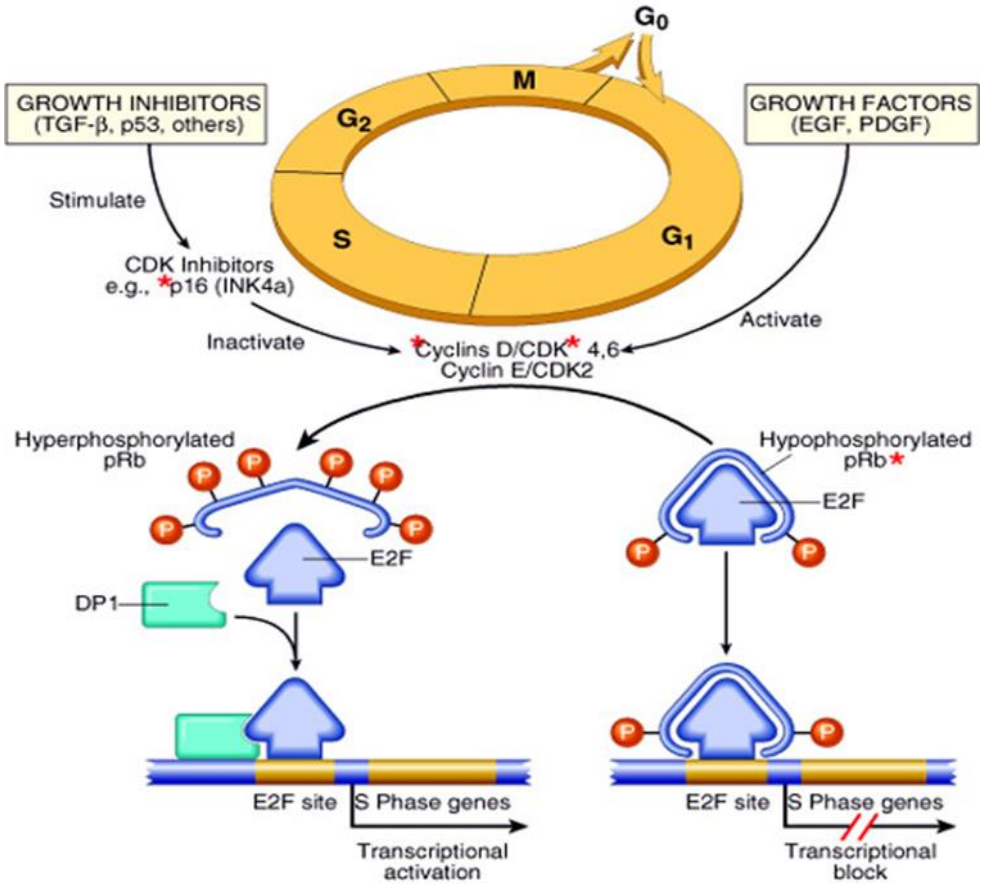
Insensitivity to growth-inhibitory signals

Tumor suppressor genes control (apply brakes to) cells' proliferation. If mutations disrupt them → cell becomes *insensitive* to **growth inhibition** → uncontrolled proliferation.

Examples: (**Rb ,TGF-b , APC , P53**)

Rb (retinoblastoma) gene:

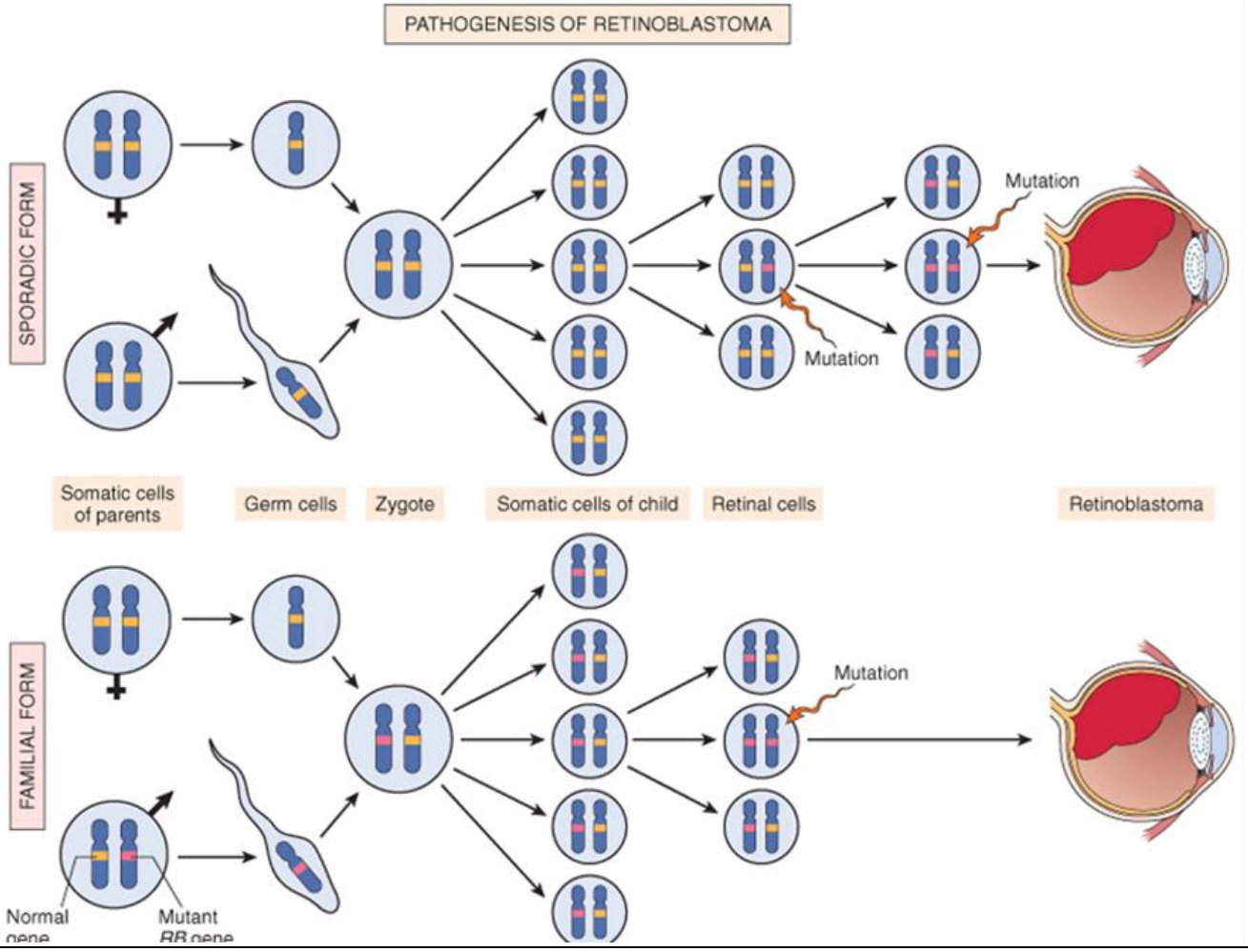
- First tumor suppressor gene discovered.
- It was discovered initially in **retinoblastomas** (this is why it is called Rb)
- Found in other tumors (**breast cancer)**
- Rb gene is a **DNA-binding protein**
- Rb is located on **chromosome 13**
- Rb gene exists in " active " and " inactive" forms.
- If active → will **stop** the advancing[33] 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**.

[33] تقدم

- Retinoblastoma is either **sporadic**[34] (60%) or **familial**[35] (40%).
- **Two mutations** required to produce retinoblastoma (will explain this shortly)
- Both normal copies of the gene should be lost to produce retinoblastoma



Transforming Growth Factor- beta pathway:

Note: all growth factors are proto oncogenes except TGF-B

- ❖ TGF-b is an **inhibitor** of proliferation.
- ❖ It regulate RB pathway.
- ❖ Inactivation of TGF-b lead to cell proliferation.

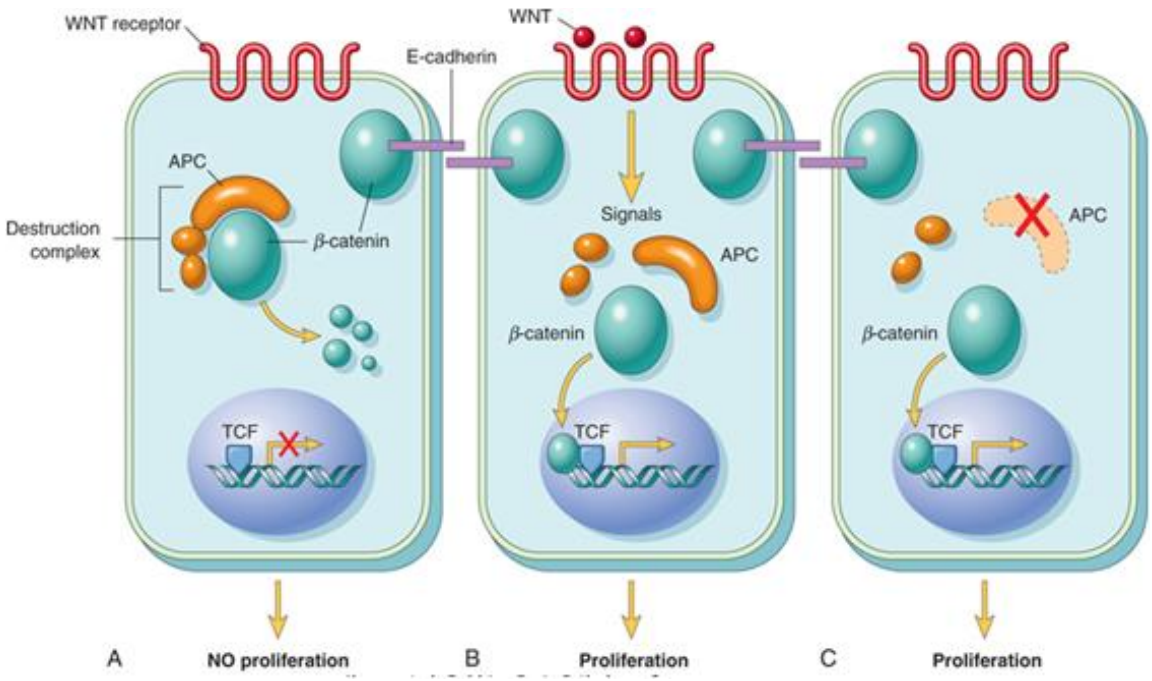
Mutations in TGF-b pathway are present in:

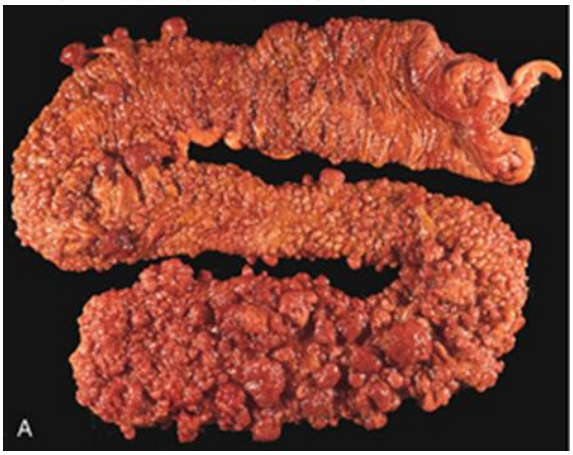
- **100%** of pancreatic cancers.
- **83%** of colon cancers.

[34] مشتت
[35] شائع في العائلة

Adenomatous Polyposis Coli – b Catenin pathway:

- APC is tumor suppressor[36] 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 thousands of **colonic polyps (Adenomatous Polyposis Coli)**





One or more of the polyps will progress to colonic carcinoma

- APC mutations are seen in 70% to 80% of **sporadic colon cancers**.

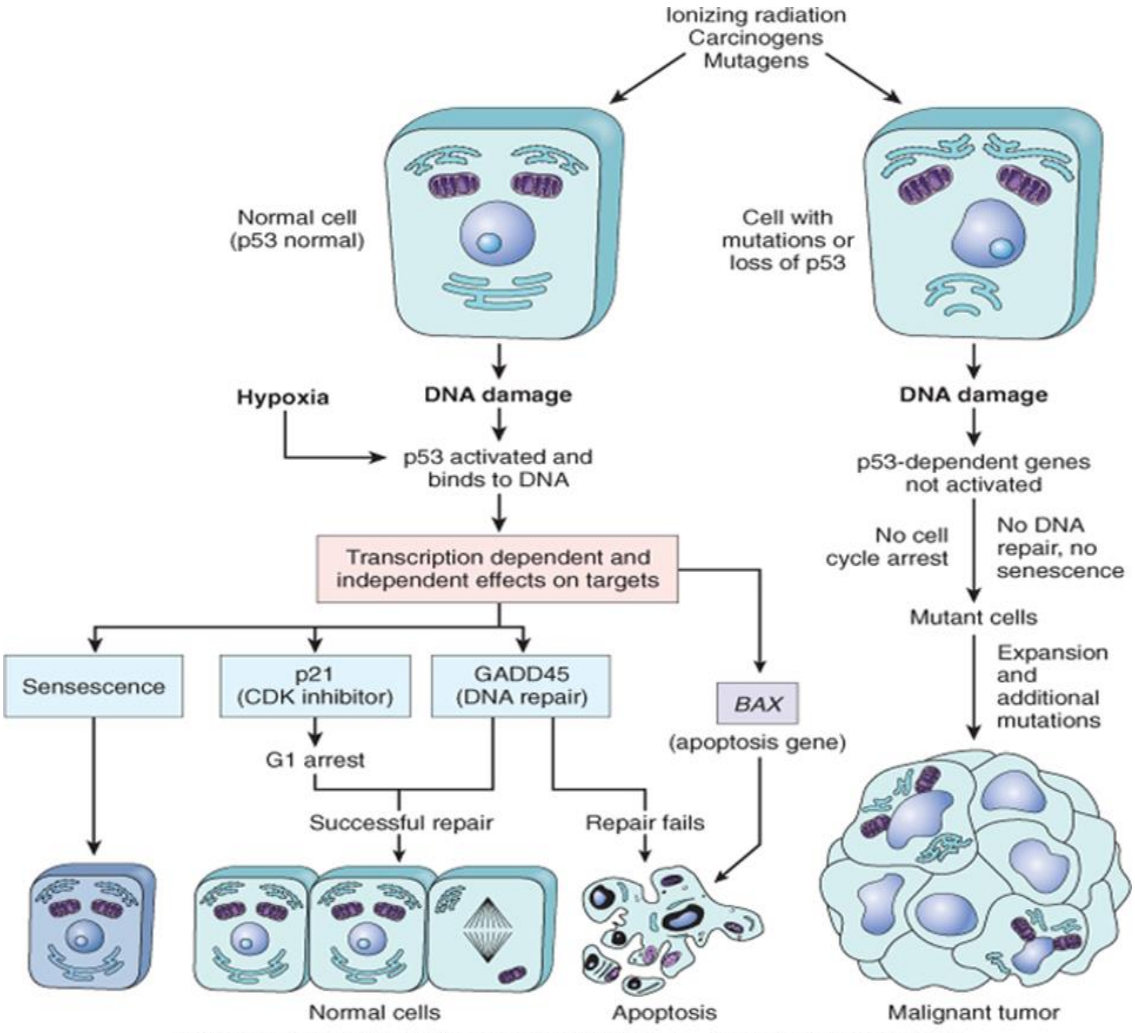
[36] قامع

P53: It has multiple functions mainly :

1. Tumor suppressor gene (anti-proliferative)
2. Regulates apoptosis

P53 senses DNA damage → Causes G1 arrest to give chance for DNA repair → Induce DNA repair genes → If a cell with damaged DNA cannot be repaired, it will be directed by P53 to undergo apoptosis.

- With loss of P53, DNA damage goes **unrepaired.**
- 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, e.g : Li-Fraumeni syndrome

We have previously said that two Rb must be effecter to produce retinoblastoma. What does this mean?

The DNA has two copies from every gene, one maternal (from mama) and one paternal (from papa). This also applies on the proto-oncogenes and the tumor suppressor genes.

The question is do I need one mutation in one allele or two mutations in both alleles to produce cancer?

Proto-oncogenes require only **one** defective allele to have a gain of function mutation.

Tumor suppressor genes require **two** defective alleles to have a loss of function mutation.

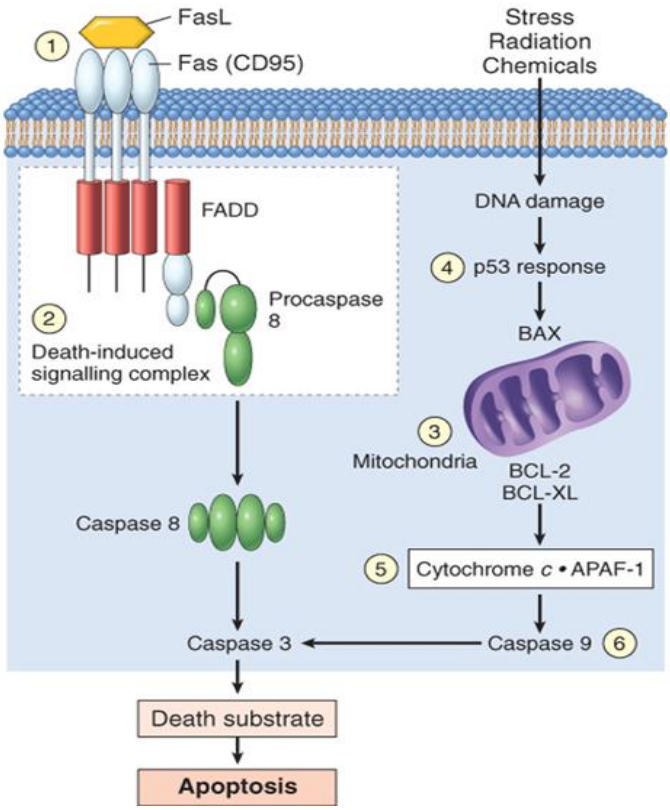
You can think of it as a car with two accelerators and two breaks. If one accelerator is "mutant" رحت وطي.

On the other hand, if one break is "mutant" you can use the other one!

If you didn't understand this just memorize the sentence or try reading this again.

Evasion of apoptosis

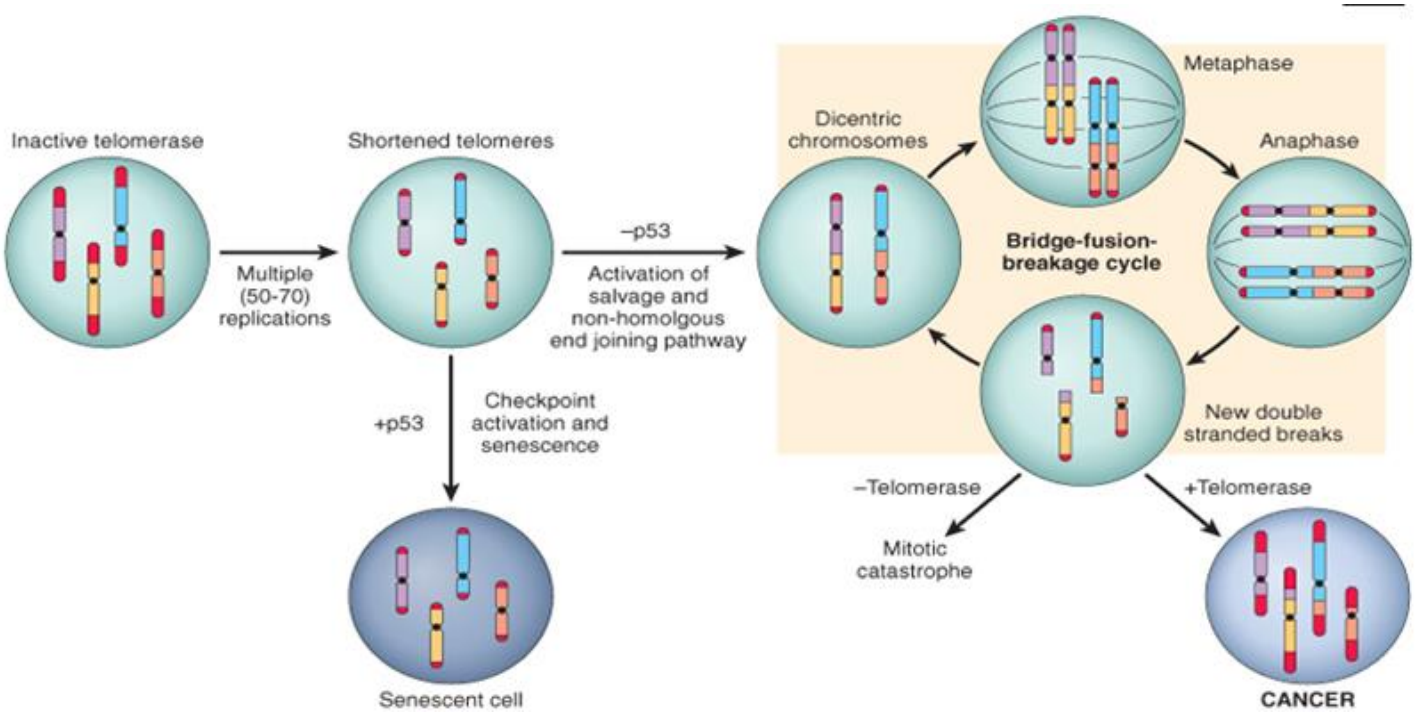
- Mutations in the **genes regulating apoptosis** are factors in malignant transformation.
- Cell survival is controlled by genes that promote and inhibit apoptosis.



- 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 e.g. **follicular lymphoma**

Limitless replicative potential

- **Normally** there is a 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.



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 telomere 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.

Sustained angiogenesis

Neovascularization has two main effects:

- Perfusion supplies oxygen and nutrients.
- Newly formed endothelial cells (in the vessel) stimulate the growth of adjacent tumor cells by secreting growth factors, e.g : **PDGF, IL-1**

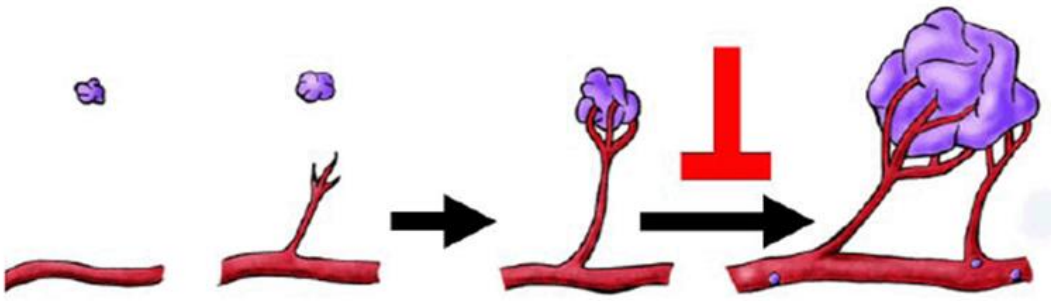
- Angiogenesis is required for **metastasis**.

How do tumors develop a blood supply?

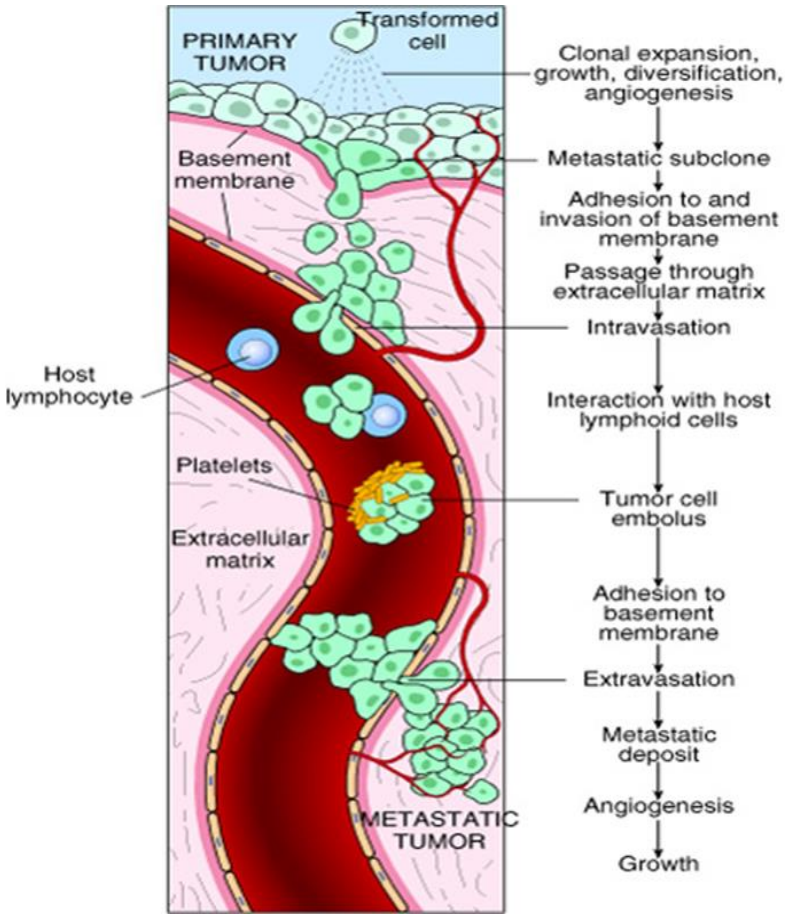
By **Tumor-associated angiogenic factors.** These factors may be produced by **tumor cells** or by **inflammatory cells** infiltrating the tumor e.g. macrophages

Important factors:

- Vascular endothelial growth factor (VEGF).
- Fibroblast growth factor.



Ability to invade and metastasize



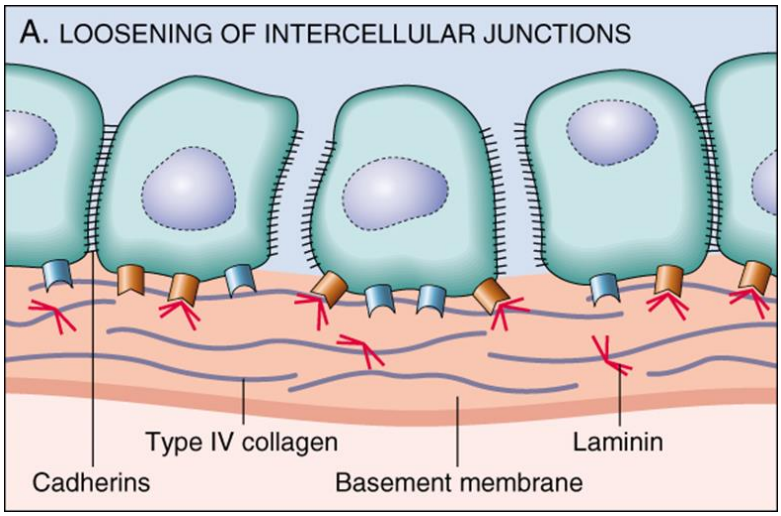
It has two phases:

- Invasion of extracellular matrix.
- Vascular dissemination and homing of tumor cells.

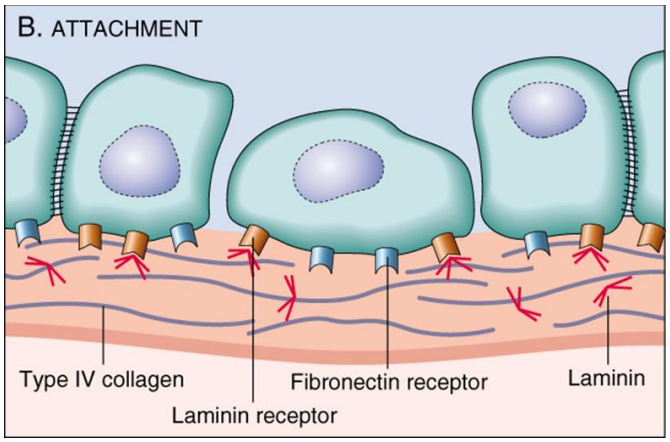
1) **Invasion of ECM:**
    - Malignant cells first breach the underlying basement membrane
    - Traverse the interstitial tissue
    - Penetrate the vascular basement membrane
    - Gain access to the circulation

Invasion of the ECM has four steps:

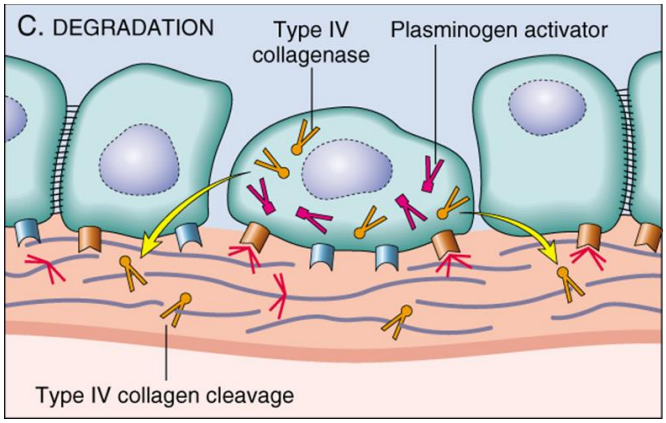
1. Detachment of tumor cells from each other.



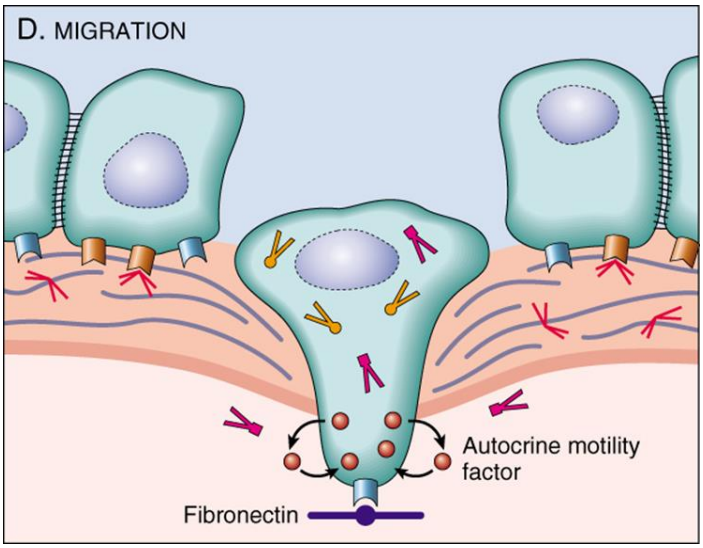
2. Attachments of tumor cells to matrix components



3. Degradation of ECM by collagenase enzyme



4. Migration of tumor cells



Vascular dissemination and homing of tumor cells:

- ❏ May form **emboli**
- ❏ Most travel as single cells.
- ❏ Adhesion to vascular endothelium.
- ❏ extravasation.

Genomic Instability

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

Examples:

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

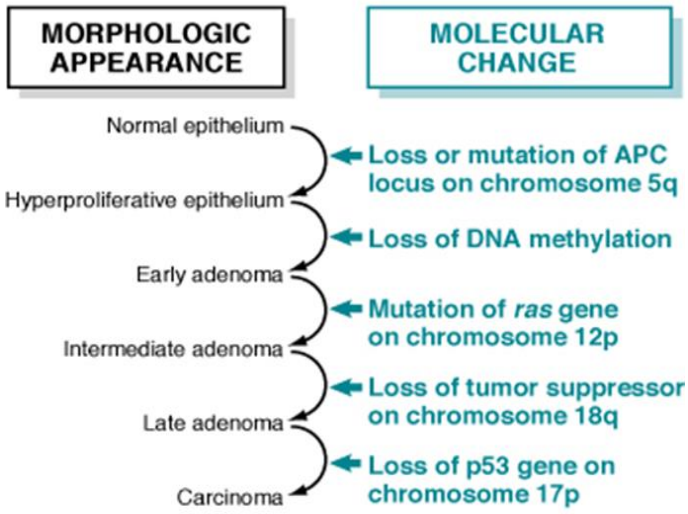
- It occurs when –When the genes are responsible of repair aren't working propperly.

Familial breast cancer:

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

Molecular Basis of multistep Carcinogenesis

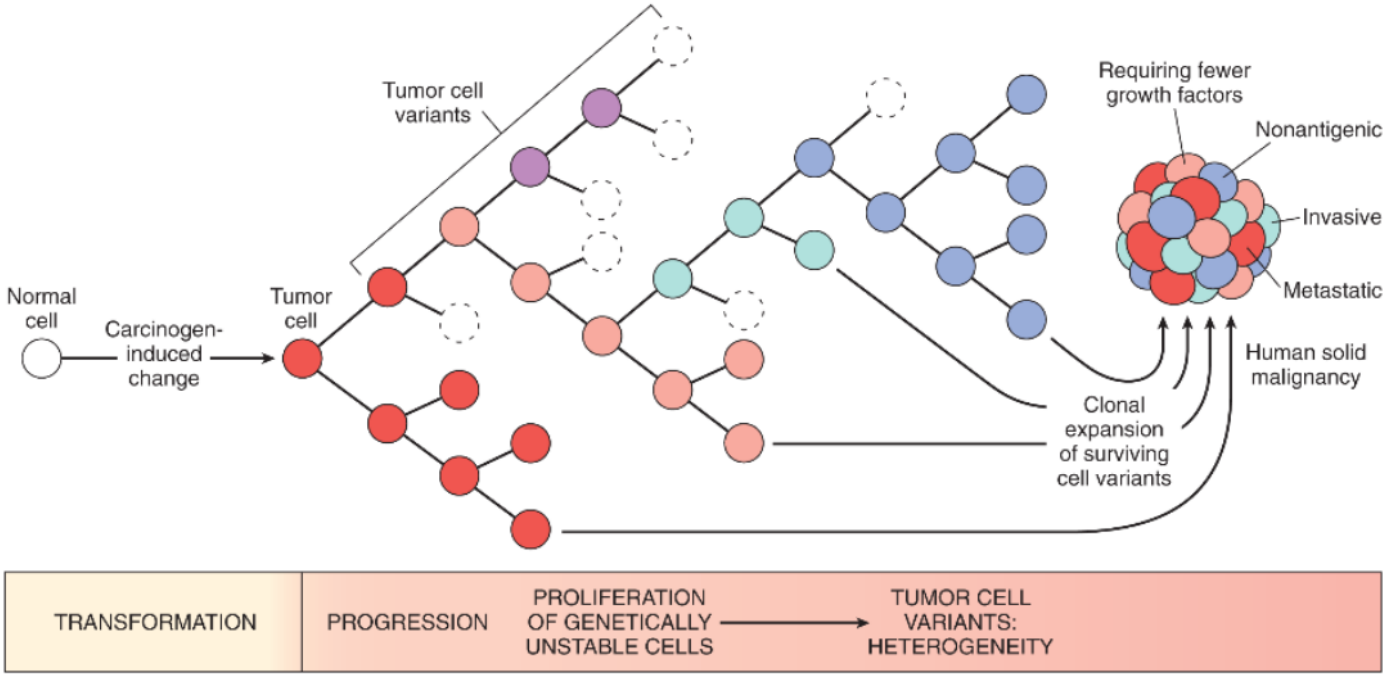
- Cancer results from **accumulation[37] of multiple mutations**
- All cancers have multiple genetic alterations, involving activation of several **oncogenes** and loss of two or more tumor **suppressor[38] genes**.



[37] تراكم
[38] قامع

Tumor progression

- **Tumor progression**[39]**:** means the tumor become more aggressive and acquires greater malignant potential due to increased mutations… not necessarily an increase in size!
- By the time the tumor becomes clinically evident[40], their constituent cells[41] are usually extremely **heterogeneous**[42]**; patients usually come late**

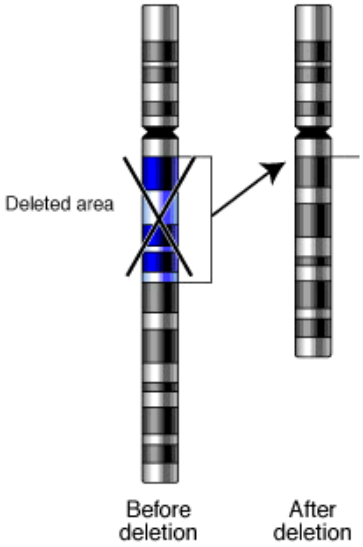


[39] تطور
[40] واضح
[41] خلاياه المكونة
[42] غير متجانسة / متغايرة الخواص

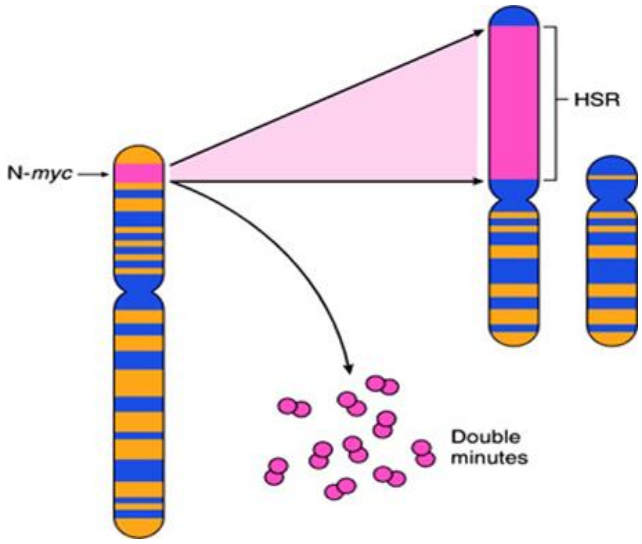
Karyotypic Changes in Tumors

- **Translocations:**
  - In **CML** : **t(9,22)** "**Philadelphia chromosome**"
  - In **Burkitt Lymphoma**: **t(8,14)**
  - In **Follicular Lymphoma**: **t(14,18)**

- **Deletions**



- **Gene amplification:**
  - Breast cancer: **HER-2**



Host defense

tumor antigen:

1- tumor *specific* antigen: found only on the tumor cells

2- tumor - *nonspecific* antigen: found on tumor cells and some normal cells

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

Where do they come from?

- Result from gene mutations: P53, RAS these mutations will be expressed on the surface of the cell and then recognized as nonself and will be attacked by the immune mechanism
- Be products of amplified genes: HER-2
- Viral antigens: from oncogenic viruses which incorporates itself with the host DNA, the resulting proteins will be expressed on the cell membrane
- Be differentiation specific: PSA[**p**rostate **s**specifi**c** **a**ntigen] in prostate Usually present late.. we look for PSA in blood if it's highly increased the patient will most likely have cancer.
- Oncofetal antigens: CEA, Alpha fetoprotein : normal embryonic antigen but absent in adults , in some tumors it will be re-expressed, e.g: colon cancer, liver cancer

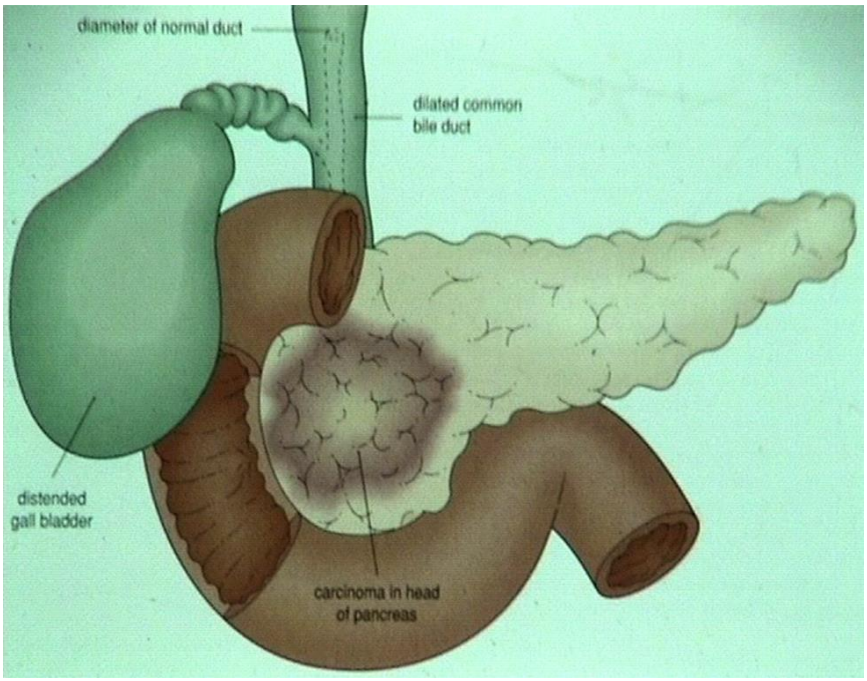
Antitumor mechanisms involve:

1. **Cytotoxic T lymphocytes (CD8) :**
    - Most efficient for killing cancer
    - cell mediated immunity
2. **Natural killer cells:**
    - cell mediated immunity.
    - antigen-antibody [type II hypersensitivity] reaction.
3. **Macrophages.**
4. **Humoral mechanisms:**
    - Complement system
    - Antibodies.

Clinical features

Tumours cause problems because:

- **Location and effects on adjacent structures: even small rumours if present in a sensitive area can be dangerous**

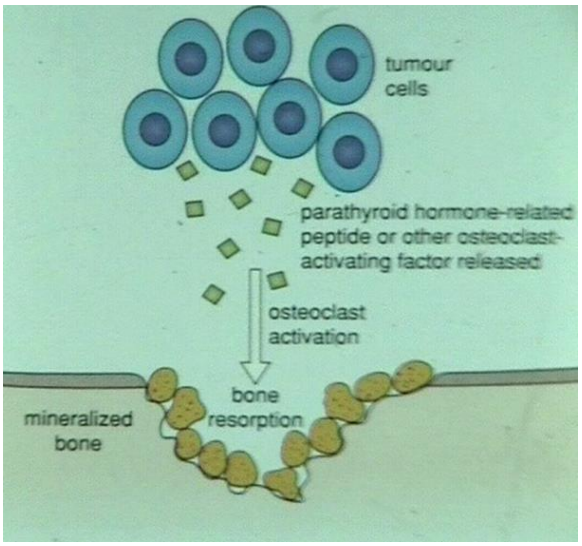


Tumor in the pancrace pressing on the bile duct

Examples :

- 1cm **pituitary adenoma** can compress and destroy the surrounding tissue and cause **hypopituitarism.**
- 0.5 cm **leiomyoma** in the wall of the renal artery may lead to renal ischemia and serious **hypertension.**

- **Tumors may cause bleeding and secondary infections.**
  - lesion ulcerates adjacent tissue and structures.



secondary fracture (pathological fracture)

Tumors can also affect functional activities:

hormone synthesis occurs in neoplasms arising in endocrine glands:

- adenomas and carcinomas of **β cells** of the islets of the **pancreas** produce **hyperinsulinism**.
- Some adenomas and carcinomas of the adrenal cortex elaborate **corticosteroids**.
  - aldosterone induced sodium retention, hypertension and hypokalemia.

- Usually such activity is associated with benign tumors more than carcinomas.

Cancer cachexia:

- Usually accompanied by **weakness**, **anorexia**[43] and **anemia**.
- Severity of cachexia, generally, is correlated with the **size** and **extent of spread** of the cancer.
- The cause of cancer cachexia are multifactorial:
  - anorexia (reduced calorie intake)
  - increased basal metabolic rate and calorie expenditure remains high.
  - general metabolic disturbance. (the body gets the glucose but it does not metabolize it fully → 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.**

[43] فقدان الشهية

- 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. مثلا مرض هوجكن قبل بسنة يصير المريض عنده حكة ما لها سبب وبعد سنة يكتشفوا ان فيه السرطان.
- They may represent significant clinical problems and may be lethal.
- They may mimic metastatic disease.

The most common Paraneoplastic syndromes are:

(Hypercalcemia - Cushing syndrome[44] - Nonbacterial thrombotic endocarditis)

The most often neoplasms associated with these syndromes:

- Lung and breast cancers and hematologic malignancies.

Paraneoplastic syndromes		
Syndrome	**Mechanism**	**Example**
Cushing's Syndrome	ACTH -like substance	Lung oat cell carcinoma
Hypercalcemia	Parathormone -like substance	Lung squamous cell carcinoma Renal cell carcinoma Breast carcinoma
Hyponatremia	Inappropriate ADH secretion	Lung oat cell carcinoma
Polycythemia	Erythropoietin -like substance	Cerebellar haemangioma Renal cell carcinoma
Trousseau's Syndrome	Hypercoagulable state	Various carcinomas
Hypoglycemia	Insulin -like substance	Various carcinomas and sarcomas
Carcinoid Syndrome	-٥hydroxy -indoleacetic acid) ٥ - HIAA (	Metastatic malignant carcinoid tumors

[44] increase in ACTH leads to increase in cortisone..

Grading and Staging

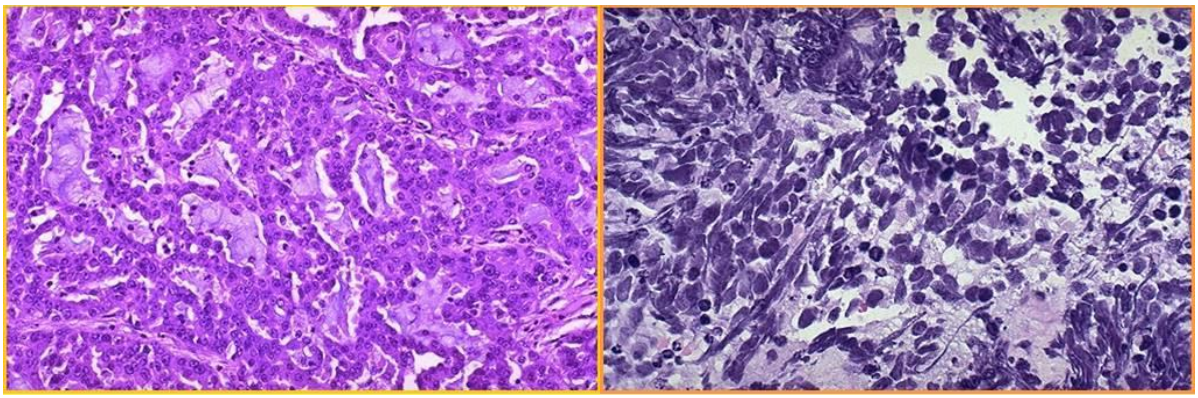
Grading: (relay on the differentiation of the cells)

- Grade I (well differentiated)
- Grade II (moderately differentiated)
- Grade III (poorly differentiated)
- Grade IV (nearly anaplastic)

* usually, the more the grade the more aggressive it is.

Staging: (the extent of the spread of neoplastic in the body)

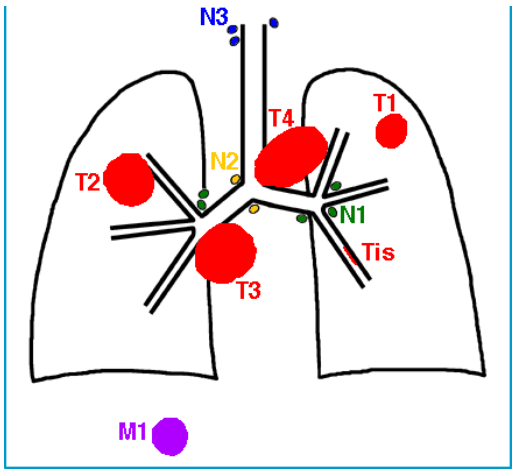
- Size.
- Regional lymph nodes involvement.
- Presence or absence of distant metastasis.
- **TNM system** (**T t**umor size .. **N** of lymph **n**ode .. **M** if there's metastasis or not)



Left: Oat cell carcinoma of the lung Undifferentiated carcinoma Grade IV
Right: Adenocarcinoma of the colon (Well differentiated carcinoma)

- 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.

TMN system in cancer:



- T (primary tumor): T1, T2, T3, T4 **the higher the number the bigger it is**
- N (regional lymph nodes): N0, N1, N2, N3 **the higher the number the farther it is**
- M (metastasis): M0, M1

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:

مثلا لو شخص سوينا له عملية ازالة ورم يختفي الانتيجين حق الورم بعدين اسوي له تحاليل كل فترة عشان اشوف الجين رجع او لا

- Useful for measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum.
- Useful in determining the <u>effectiveness of therapy and detection of recurrences after excision.</u>
- 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 ,<u>prognosis</u> and <u>modification of treatment</u>)

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

Example: detection of **BCR-ABL** transcripts in **<u>chronic myeloid leukemia.</u>**

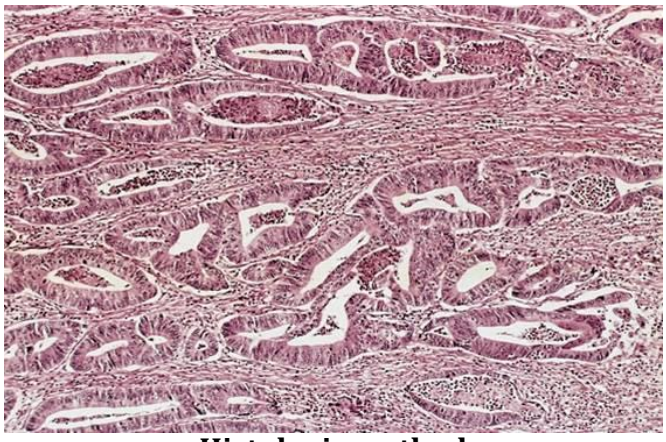
- **Fluorescent in situ hybridization (fish)**:

it is useful for detecting chromosomes translocation characteristic of many tumors

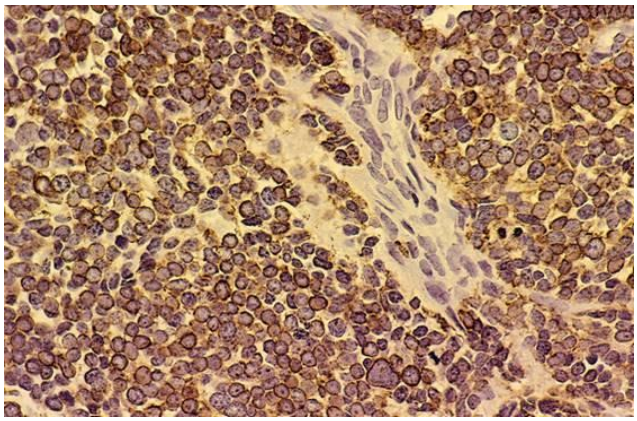
Both PCR and Fish can show amplification of oncogenes (HER2 and N-MYC)

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)
    - fine-needle aspiration.
    - Cytologic smears.



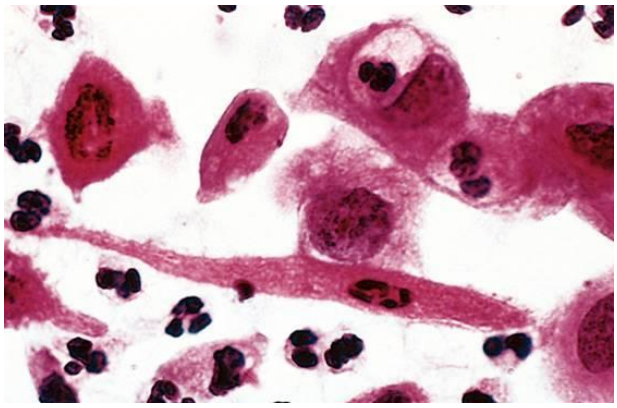
Histologic method



Immunohistochemistry (antigen antibody reactions)

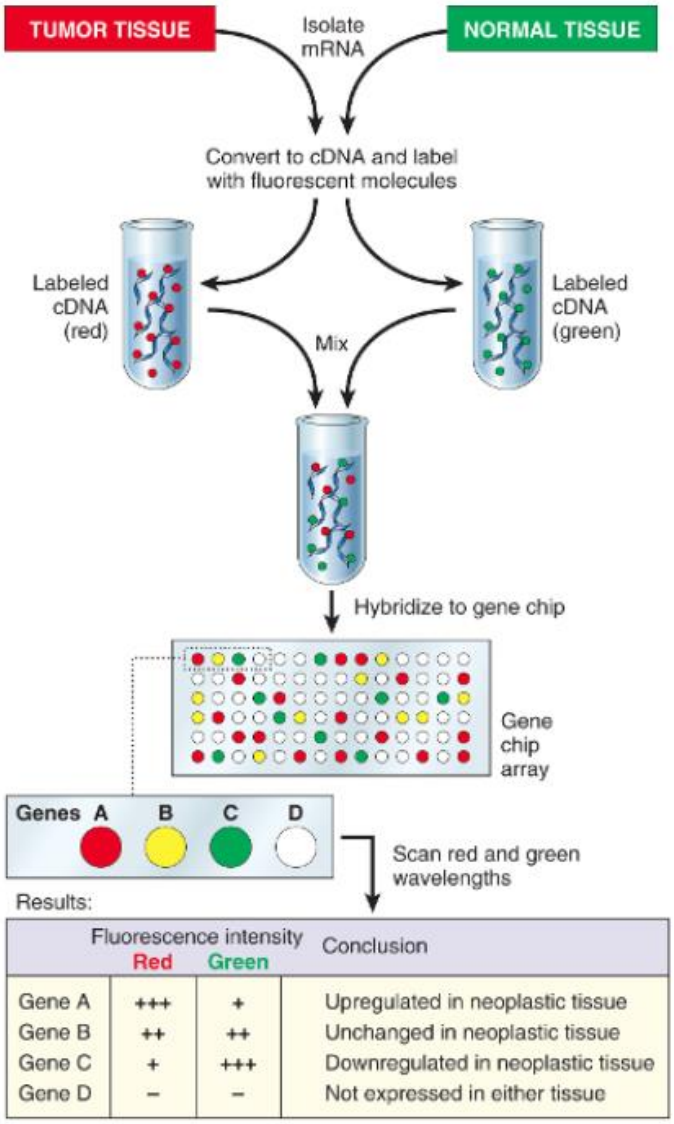
if the tissue is extremely undifferentiated then we put antibodies and look for positive reactions with the antigens , these antigenic expressions specify exactly which cancer cell it is

*the dark parts are positive and the light ones are negative



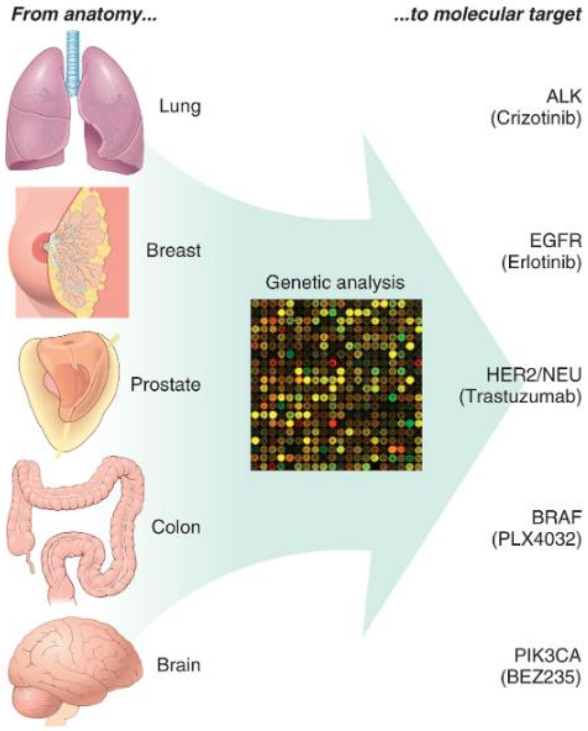
Cytopathology

- **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.

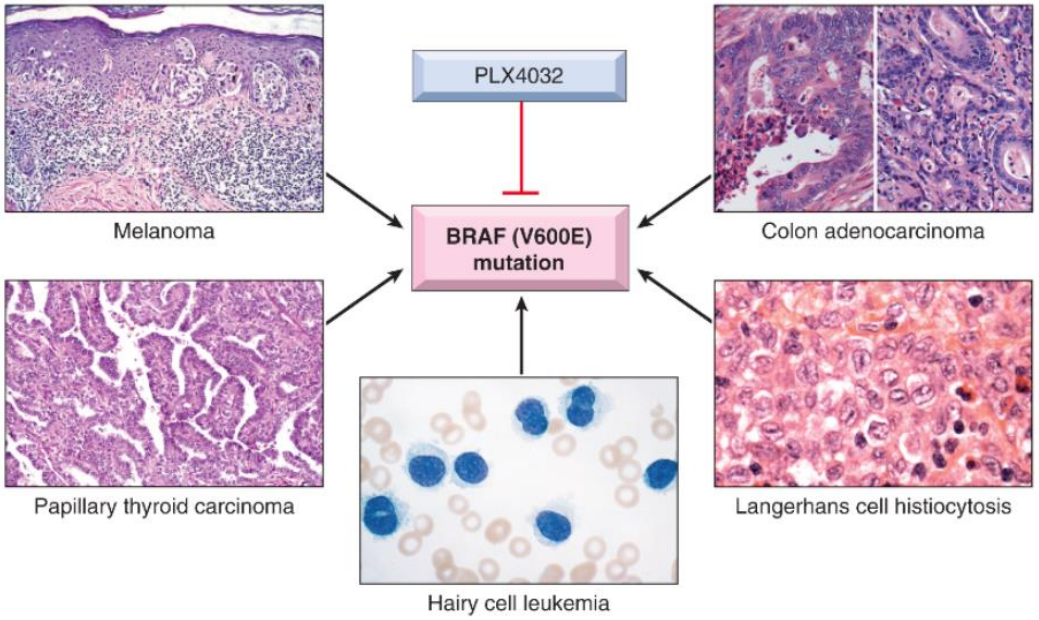


the mRNA is extracted from any two sources then they are synthesized in vitro with fluorescently labeled nucleotides .after that, they are hybridized onto a chip with different probes. we put this chip under a high resolution laser. the spots express different fluorescent intensities .

- according to the expression we can give targeted therapy



genetic analysis provides targeted therapy against (ALK / EGFR / HER2 / BRAF / PIK)



same inhibitors are used tackle different tumors.

providing treatment for a specific type of cancer regardless of the histological difference (diverse tumor types that share a common mutation , BRAF , may be candidates for treatments with the same drug , PLX)

SUMMARY

Laboratory Diagnosis of Cancer

- Several sampling approaches exist for the diagnosis of tumors, including excision, biopsy, fine-needle aspiration, and cytologic smears.
- Immunohistochemistry and flow cytometry studies help in the diagnosis and classification of tumors, because distinct protein expression patterns define different entities.
- Proteins released by tumors into the serum, such as PSA, can be used to screen populations for cancer and to monitor for recurrence after treatment.
- Molecular analyses are used to determine diagnosis, prognosis, the detection of minimal residual disease, and the diagnosis of hereditary predisposition to cancer.
- Molecular profiling of tumors by cDNA arrays and sequencing can determine expression of large segments of the genome and catalog all of the mutations in the tumor genome and thus may be useful in molecular stratification of otherwise identical tumors or those of distinct histogenesis that share a mutation for the purpose of treatment and prognostication.

MCQ's

1- A 44-year-old woman notes a lump in her left breast while taking a shower. Her physician notes a 3 cm firm, irregular, non-movable mass located in the upper outer quadrant of her left breast on physical examination. A fine needle aspiration of this mass is performed. Cells obtained from the mass are examined cytologically and are consistent with infiltrating ductal carcinoma. The mass is removed with lumpectomy along with an axillary lymph node dissection. Which of the following findings will best predict a better prognosis for this patient?

A. The tumor cells are strongly estrogen receptor positive.
B. No metastases are found in the sampled lymph nodes.
C. Flow cytometric analysis demonstrates aneuploidy and a high S-phase.
D. She has one relative who had a similar type of breast cancer.
E. The tumor has a high grade.

2- A 45-year-old healthy woman has a routine check of her health status. She has no chest pain, cough, or fever. A chest x-ray taken and shows a peripheral 2.5 cm diameter "coin lesion" in the right mid-lung field. Which of the following biologic characteristics best distinguishes this lesion as a neoplasm, rather than a granuloma?

A. Recurrence following excision
B. Rapid increase in size
C. Sensitivity to radiation or chemotherapy
D. Uncontrolled (autonomous) growth
E. Necrosis

3- A 48-year-old woman goes to her physician for a routine physical examination. A 4 cm diameter non-tender mass is palpated in her right breast. The mass appears fixed to the chest wall. Another 2 cm non-tender mass is palpable in the left axilla. A chest radiograph reveals multiple 0.5 to 2 cm nodules in both lungs. Which of the following classifications best indicates the stage of her disease?

A. T1 N1 M0
B. T1 N0 M1
C. T2 N1 M0
D. T3 N0 M0
E. T4 N1 M1

4- A study is performed to analyze characteristics of malignant neoplasms in biopsy specimens. The biopsies were performed on patients who had palpable mass lesions on digital rectal examination. Of the following microscopic findings, which is most likely to indicate that the neoplasm is malignant?

A. Pleomorphism
B. Atypia
C. Invasion
D. Increased nuclear/cytoplasmic ratio
E. Necrosis

5- Review of a series of surgical pathology reports indicates that a certain type of neoplasm is graded as grade I on a scale of I to IV. Clinically, some of the patients with this neoplasm are found to be stage I. Which of the following is the best interpretation of a neoplasm with this stage I designation?

A. Is unlikely to be malignant
B. Has probably arisen from epithelium
C. May spread via lymphatics
D. Has an in situ component
E. Is well-differentiated and localized

6- A child is born with a single functional allele of a tumor suppressor gene. At the age of five the remaining normal allele is lost through a point mutation. As a result, the ability to continue the transition from G1 to the S phase of cell cycle is lost. Which of the following neoplasms is most likely to arise via this mechanism?

A. Infiltrating ductal carcinoma of breast
B. Small cell anaplastic carcinoma of the lung
C. Retinoblastoma of eye
D. Cerebral astrocytoma
E. Chronic myeloid leukemia

7- A 50-year-old man has felt vague abdominal discomfort for the past 4 months. On physical examination he has no lymphadenopathy, and no abdominal masses or organomegaly can be palpated. Bowel sounds are present. An abdominal CT scan shows a 20 cm retroperitoneal soft tissue mass obscuring the left psoas muscle. A stool specimen tested for occult blood is negative. Which of the following neoplasms is this man most likely to have?

A. Melanoma
B. Hamartoma
C. Adenocarcinoma
D. Lymphoma
E. Liposarcoma

8- A 52-year-old man has had increasing fatigue for the past 6 months. On physical examination he has a palpable spleen tip. Laboratory studies show a WBC count of 189,000/microliter. The peripheral blood smear shows many mature and immature myeloid cells present. Cytogenetic analysis of cells obtained via bone marrow aspiration reveals a t(9:22) translocation. This translocation leads to formation of a hybrid gene that greatly increases tyrosine kinase activity. Which of the following genes is most likely translocated to cause these findings?

A. p53
B. Rb
C. c-abl
D. NF-1
E. k-ras

Answers:
1-B
2-D
3-E
4-C
5-E
6-C
7-E
8-C

Q1) Identify the types of carcinoma that can result from infection with the following DNA viruses.

1- **Epstein –Barr virus (EBV)**

Burkitt lymphoma, nasopharyngeal cancer.

2- **Human papillomavirus (HPV)**

Cervical cancer

3- **Hepatitis B**

Hepatocellular cancer

Q2) What is retrovirus?

An RNA virus that replicates by forming DNA via reverse transcriptase.

Q3) Name the following tumors:

Benign tumor of glandular breast tissue:

Breast cancer

Benign tumor of bone:

Osteoma

Malignancy of bone:

Osteosarcoma

Done by:

محمد الخراز
مها الربيعة
حنان محمد
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Best wishes.. Pathology team 434

We recommend for you:

Kevin Mangum YouTube channel for Pathology:
https://www.youtube.com/playlist?list=PLvV8q1_i8UrbxxvLqtwgKLEE5DSVD2SGd

Dr. Najeeb Lectures:
http://www.drnajeeblectures.com/