لرجوع للعمل وحده لا يغني عن الرجوع للمصادر الأساسية

MEDICINE
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 436

NEOPLASIA

- Definitions: neoplasm, tumor, oncology.
- Classification of tumors into benign and malignant.
- Nomenclature of tumors.
- Characteristics of benign and malignant 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.
- Define the terms: dysplasia & carcinoma in situ.
- 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.
- 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.
- 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.

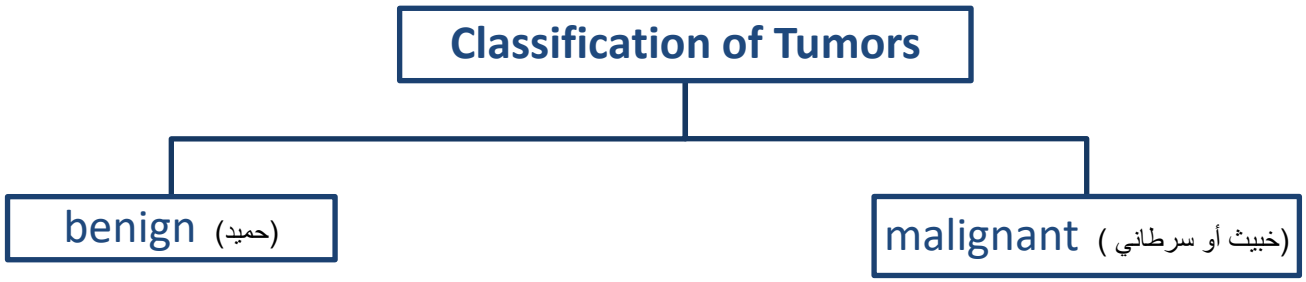
Definitions: blue
Examples: green
Doctor's note: red
Extra explanation: grey
Diseases names: Highligh

Definitions

- Neoplasia: **literally means "new growth."**
- Neoplasm = **tumor**
- Tumor = **swelling (in the clinical settings, tumor is usually used interchangeably with neoplasm)**
- Oncology= **The study of tumors. (Oncos = tumor) + (ology = study of)** العلم الذي يعنى بدراسة الأورام

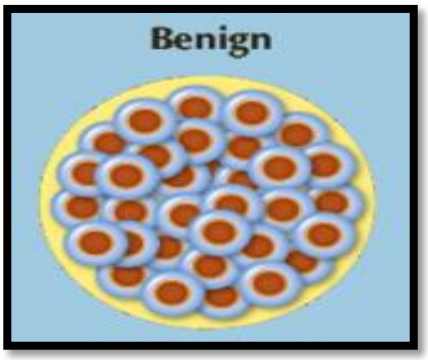
Classification of Tumors

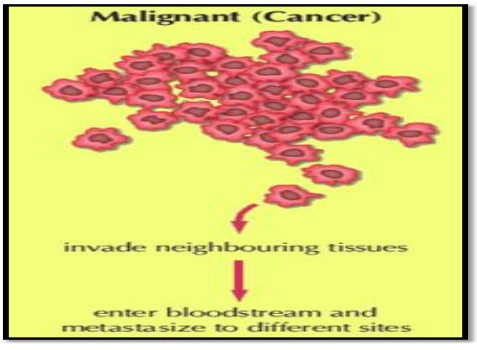
The division of neoplasms into benign and malignant categories is based their potential clinical behavior.



- Benign: **the microscopic and gross characteristics of the lesion are considered to be relatively innocent.**
- Malignant: **lesions can invade and destroy adjacent structures and spread to distant sites (metastasize) to cause death.**
- (Metastasize): انتقال الورم إلى أماكن آخرى وهي أهم ميزة للتفريق بين الورم الخبيث والحميد.

Benign	malignant
Tumors remain localized	**Can invade and destroy adjacent structures**
Tumors are amenable to local surgical removal.	**Causes death - if not treated**
Patients generally survive.	**Dangerous tumor**





All tumors, benign and malignant, have two basic components:

Note:
وهي الخلايا اللي تكاثرت وكونت ال tumor

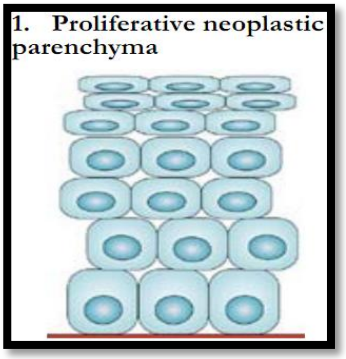
1. The parenchyma: made up of **transformed or neoplastic cells.**

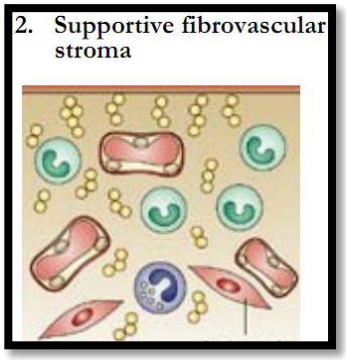
-Determines the biological behavior of the tumor.
-From which the **tumor derives its name.**

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

ال stroma: هي الenvironment اللي يعيش فيها الورم وهي مهمة بالنسبة له لأنه لا يستطيع النمو والعيش بدونها

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





Nomenclature of tumors

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

1- Benign tumors.

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

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

-**examples:**
Rhabdomyoma: Benign tumor arising in skeletal muscle.
Leiomyoma: Benign tumor arising in smooth muscle.

The nomenclature of mesenchymal **(connective tissue)** tumors usually apply this rule.
e.g.
Fibroma: a benign tumor arising in fibrous tissue.
Chondroma: a benign tumor arising in cartilaginous tissue.
Osteoma: a benign tumor arising in bone tissue.
Lipoma: Benign tumor arising in fatty tissue.

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

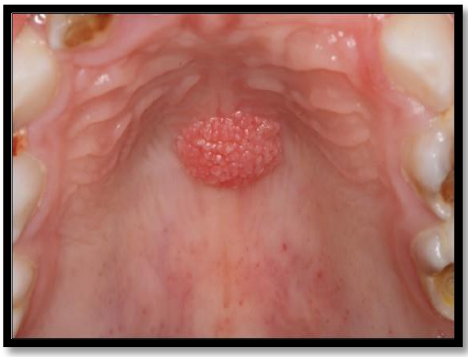
يعني هذي تسميتها تشبه تسمية Benign tumors ولكن هذي الأمثلة فوق مستثناة من القاعدة وتصنف على إنها Malignant tumors

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

Exception for (epithelial benign tumors). They are classified on the basis of:
-The cell of origin
-Microscopic pattern.
-Macroscopic pattern.

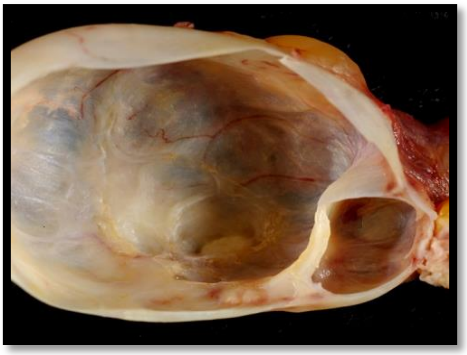
examples:
1-Adenoma: (adeno = gland) benign epithelial neoplasms
a) producing a glandular pattern.
b) OR derived from glands (not necessarily producing glandular structures).

2-Papilloma: Benign epithelial neoplasms producing microscopically or macroscopically **visible finger-like** or warty projections from epithelial surfaces.

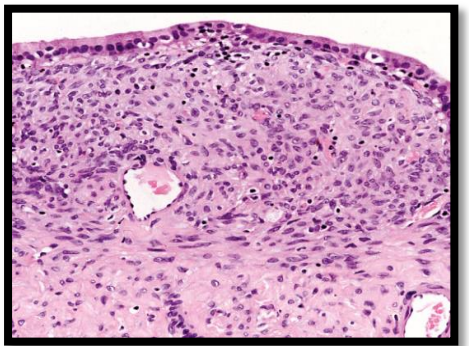


3-cystadenomas: Benign epithelial neoplasms forming large cystic masses, as in the ovary.

Cystadenoma – Macroscopically



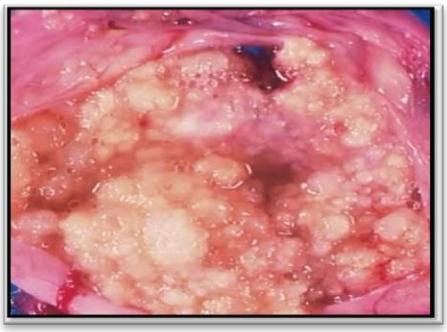
Cystadenoma – Microscopically



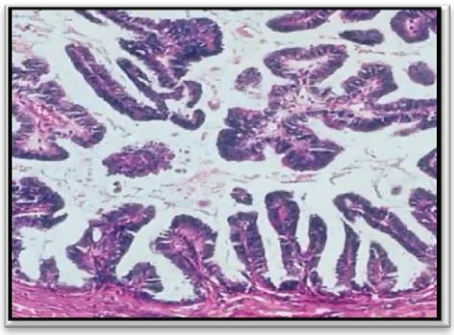
4-papillary cystadenomas: Benign epithelial neoplasms forming large cystic masses also produce papillary patterns that protrude into cystic spaces.

ملاحظة: تشبه الcystadenomas في تكوين التكيّس لكن تختلف في وجود نتوءات في داخل التكيس لذلك أضيفت كلمة papillary في البداية

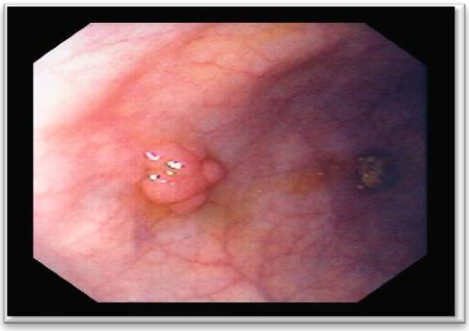
Papillary cystadenoma – Macroscopically

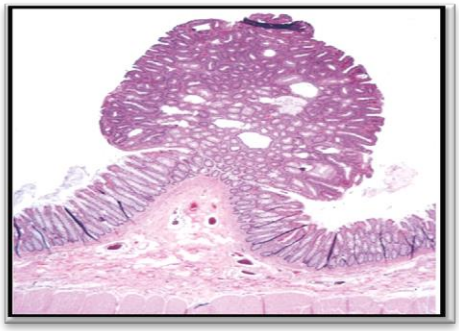


Papillary cystadenoma – Microscopically



- Polyp: a mass that projects above a mucosal surface, as in the gut (الأمعاء) , to form a macroscopically visible structure.





2- Malignant tumors.

1. Malignant neoplasms arising in **mesenchymal tissue: SARCOM**.
   Note: mesenchymal tissue = **(connective tissue)**

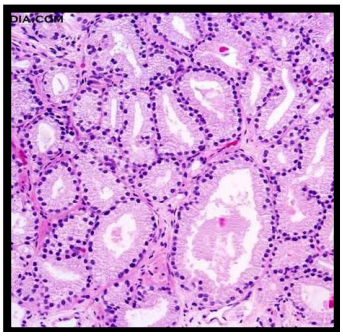
2. Malignant neoplasms arising from **epithelial origins: CARCINOMA**.

A-*Sarcomas* includes:

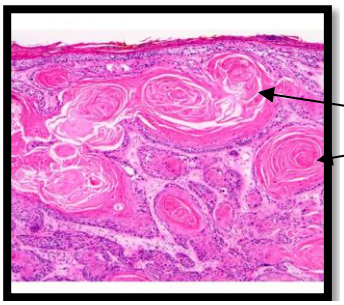
1-Fibrosarcoma: a malignant tumor arising in fibrous tissue.
2-Chondrosarcoma: a malignant tumor arising in cartilaginous tissue.
3-Osteosarcoma: a malignant tumor arising in bone tissue.
4-Liposarcoma: a malignant tumor arising in fatty tissue.

B-*Carcinomas includes:*

1-Carcinomas that are derived from glandular epithelial cells (**whether forming glands or not**): **adenocarcinomas.**



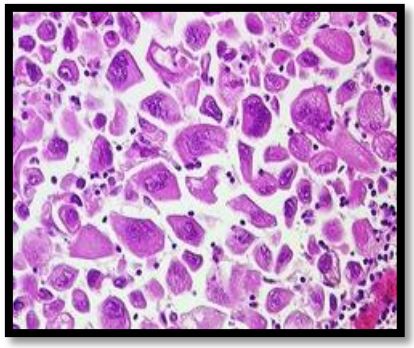
2-Carcinomas that are derived from squamous cells (**sometimes producing keratin**): **squamous cell carcinomas.**



3-Carcinomas that **show little or no differentiation** and must be called **poorly differentiated or undifferentiated carcinoma.**

يعني ما نعرف نوعه ولا اسم الtissue اللي طالع منه

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



يعني لو كان التيومر طالع من Epithelial cells
نسميه (**Undifferentiated Carcinoma**)

اما لو مانعرف من وين طالع نسميه:
(**Undifferentiated malignant tumor**)

3- Mixed tumors.

The **transformed cells** in a neoplasm, whether benign or malignant, often resemble each other, as though all had been **derived from a single progenitor** **(يعني تطلع من نفس المكان)**, consistent with the monoclonal origin of tumors.

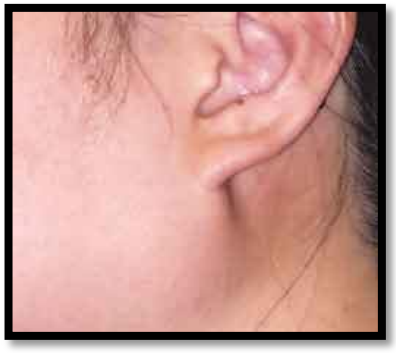
In some unusual instances, however, *divergent differentiation* of a single neoplastic clone along two lineages (يعني تنقسم وتعطيك أكثر من نوع تيومر), creating so-called *mixed tumors*.
يعني بالمختصر الخلايا اللي تكون التيومر تنشأ من نفس المكان ولكن عند الانقسام تعطي أكثر من نوع من التيومر.

The best example is mixed tumor of **salivary gland**. These tumors have obvious **epithelial components** dispersed throughout a fibromyxoid stroma (**mesenchymal components**), sometimes harboring islands of cartilage or bone.

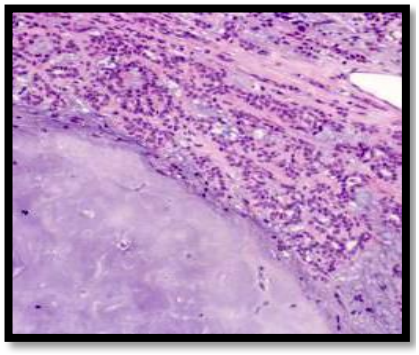
All of these diverse elements are thought to **derive from, a single clone** capable of giving rise epithelial cells or myoepithelial cells, or both, and the preferred designation for these neoplasms is ***pleomorphic adenoma***.
**Pleomorphic=* متعددة الأشكال

e.g. of *pleomorphic adenoma:*

Macroscopically



Microscopically



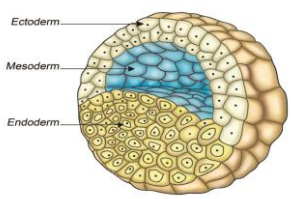
Definitions

Teratoma: 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**.

Extra information للتوضيح

Germ cell layer : هي مجموعة الخلايا التي تنتج من عملية التكوين الجنيني ، ومنها تتكون جميع الأنسجة والأعضاء. هناك ٣ طبقات كل منها سيكون مسؤول عن إنتاج أعضاء معينة

١-Endoderm
٢-Mesoderm
٣-Ectoderm



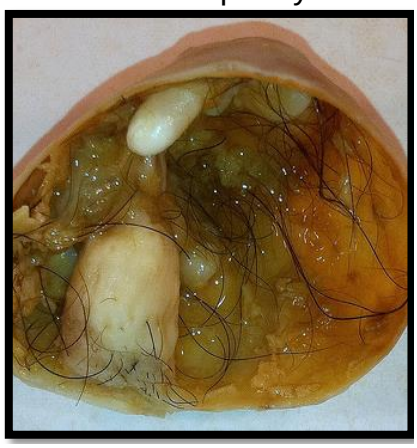
- Teratomas originate from **totipotential cells** such as those normally present in the ovary and testis and sometimes abnormally present in sequestered *midline embryonic rests.* Such cells have the capacity to differentiate into any cell type found in the adult body.

totipotential cells: an embryonic cell that is capable of developing into any variety of body cells.

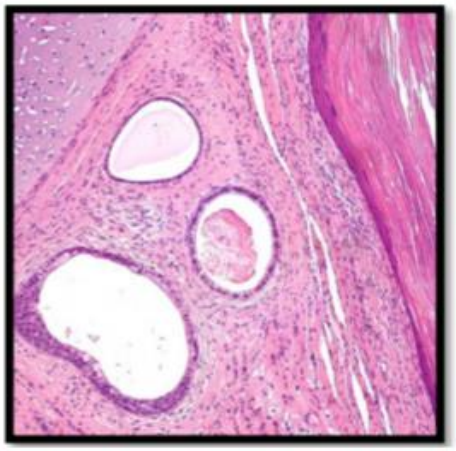
-When all the components within the teratoma are well differentiated, it is a benign (mature) teratoma.
-However, when they are less differentiated, it is an immature, potentially or overtly, malignant teratoma.

اختصارا للأربع سطور اللي فوق
Benign → (mature) teratoma.
Malignant → (immature) teratoma.

Macroscopically



Microscopically



Hamartoma: is a **mass of disorganized** benign-looking tissue indigenous to the particular site.

-For example, *pulmonary chondroid hamartoma,* which contains **islands of disorganized**, but **histologically normal cartilage, bronchi, and vessels.**

-Hamartomas have traditionally been considered developmental **malformations**, but some genetic studies have shown the presence of acquired translocations, suggesting a neoplastic origin.

Choristoma: is a congenital anomaly consisting of a heterotopic rest of cells.

تعريف آخر أوضح:
a mass composed of normal cells in a different location(يعني موقعه غلط) .

-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.

-Choristoma **has usual trivial significance.**

Characteristics of benign and malignant tumors.

(objectives غير موجودة في السلايدات لكن موجودة في ال **)**

How to tell a benign and malignant tumor apart?

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

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.**

Table 5–1 Nomenclature of Tumors

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

Differentiation and anaplasia

Definition:

the extent to which the parenchymal cells of the tumor resemble their normal counterparts morphologically and functionally

NOTE: Differentiation &anaplasia seen only in **parenchymal cells**.

tumors might be:

- well differentiated = closely resemble their normal counterparts
- Moderately differentiated
- Poorly differentiated
- Undifferentiated (Anaplasia)

Note: anaplasia is hallmark of malignancy.

Benign tumor:

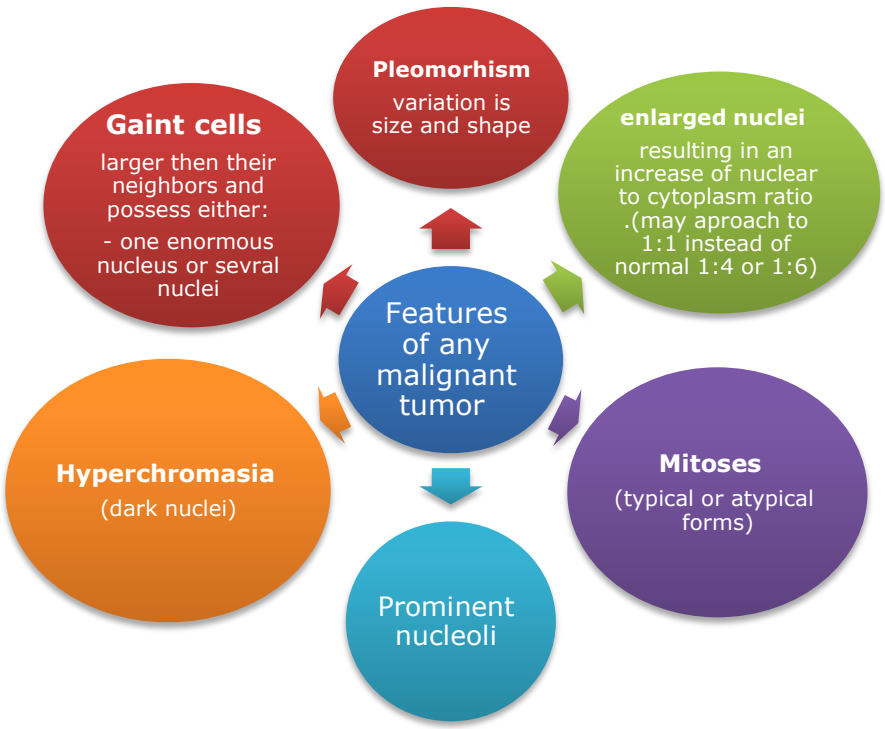
- **Well differentiated only.**
- **Mitoses are usually rare.**

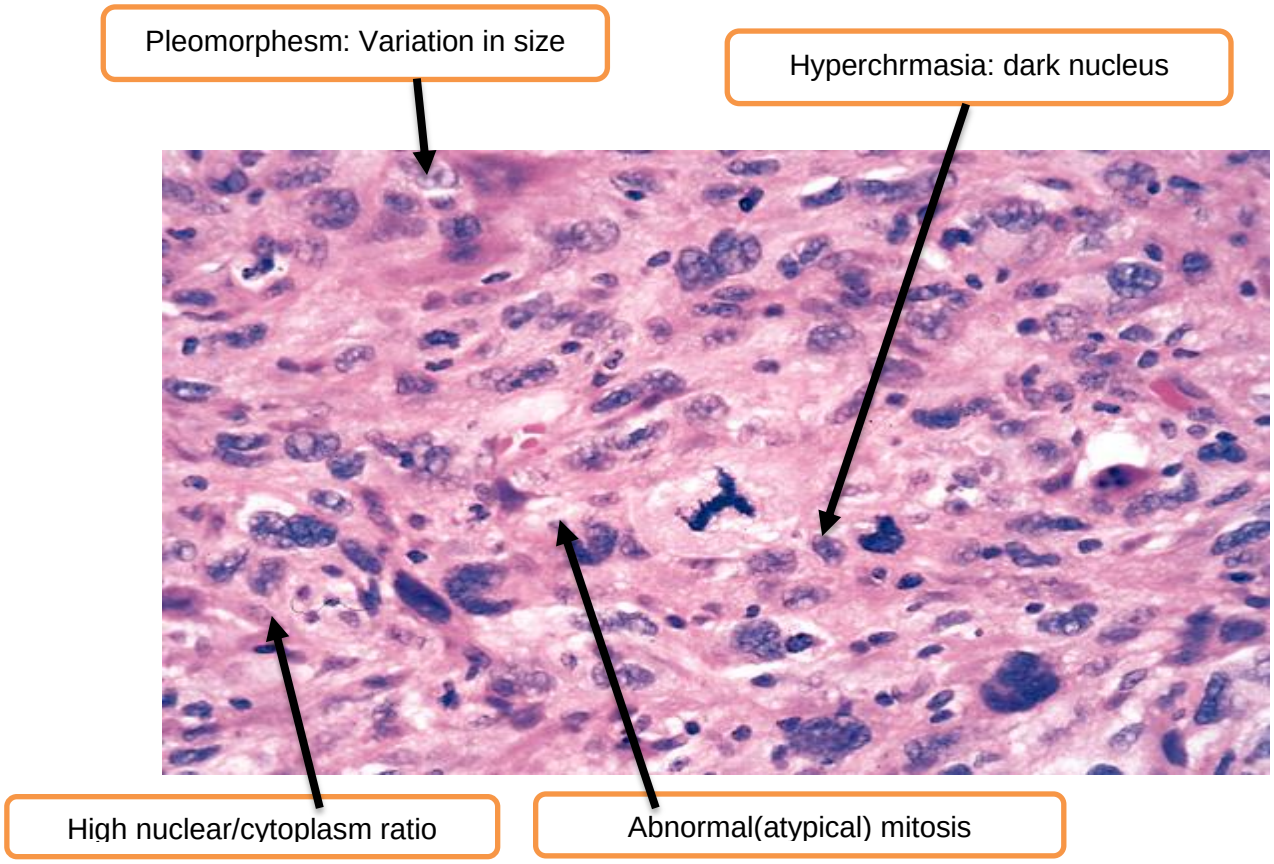
Malignant tumor can be :

- **Well differentiated** ⟶ **Undifferentiated**

NOTE: the more differentiated the tumor cells the more completely it retains the functional capabilities of its normal counterparts**.**
Ex: benign neoplasms and even will differentiated cancers of endocrine glands frequently elaborate the hormones characteristic of the origin.

Signs of malignancy under the microscope:





Rate of growth:

- Benign tumors:
  - grows slowly.
  - are affected by blood supply, hormonal effects, location.

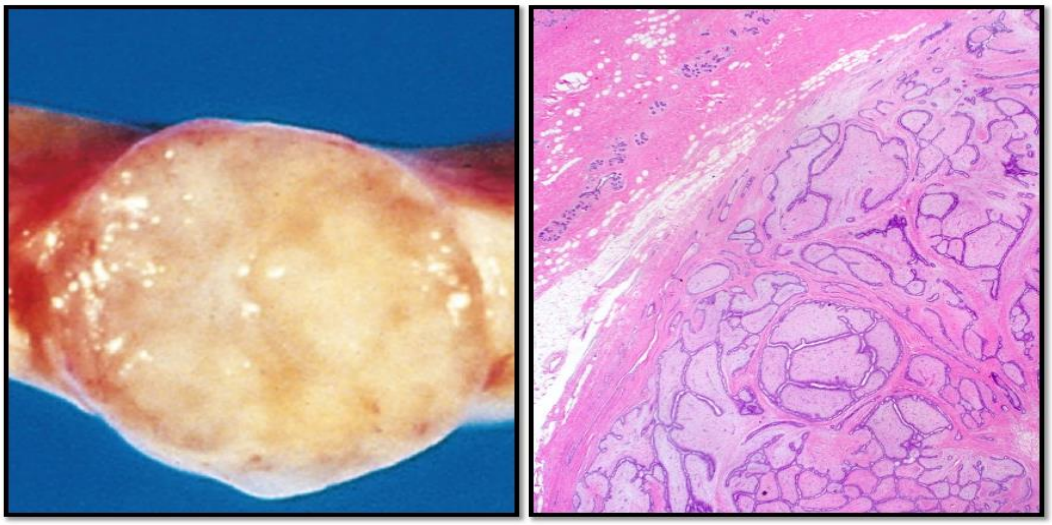
(ex. of hormonal effect: leiomyoma of uterus and fibro-adenoma of the breast are under the effect of Progesterone and estrogen)

- Malignant tumors :
  - grows faster.
  - Correlate with the level of differentiation.

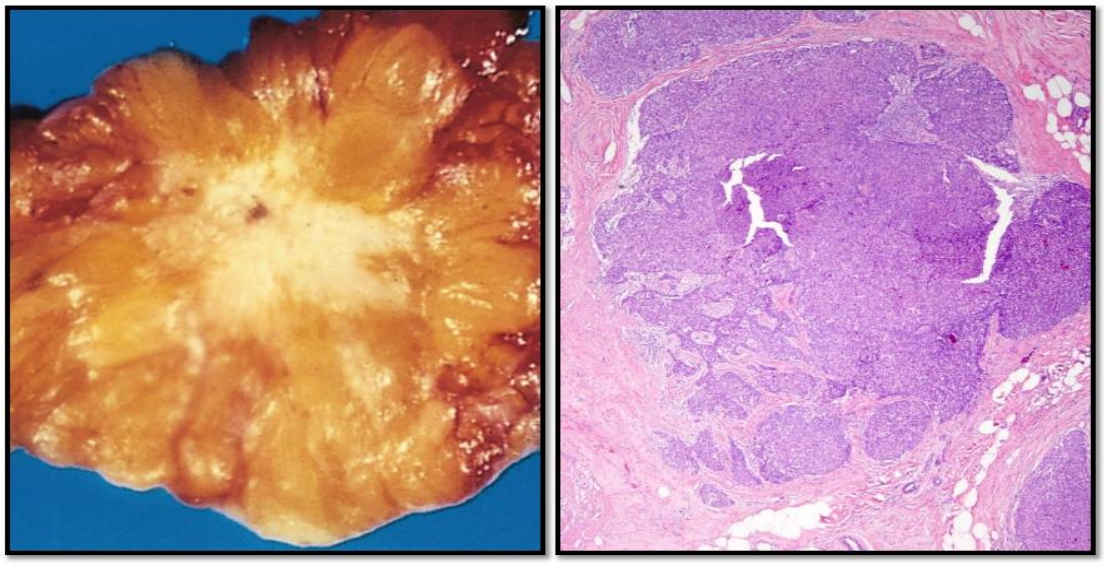
NOTE: the more tumor is less differentiated (more anaplastic) the faster it grows.

Local invasion:

- Benign tumors :
  - Remain localized
  - Cannot invade
  - Usually capsulated



- Malignant tumors:
  - Progressive invasion (invade underlying basement membrane or stroma)
  - Destruction
  - Usually not capsulated



Metastasis

Definition:

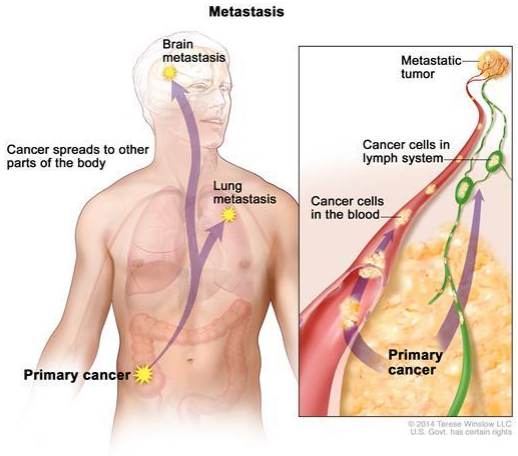
it is the development of secondary implants of a tumor that are discontinuous with the primary tumor, possibly located in remote tissues.(قدرة الورم على الانتشار)

(اول مكان يطلع فيه التيومر يعتبر برايمري والسكندري هو مكان انتشاره)

More than any other attribute, the property of metastasis identifies a neoplasm as malignant.

Features:

- Cancer have different ability to metastasize.
- Approximately 30% patients present with clinically evident metastases.
- Generally, the more anaplastic and the larger the primary tumor, the more likely it metastasizes.



Pathways to spread:

- lymphatic spread.
- hematogenous spread (by blood vessels).
- seeding of the body cavities.

Lymphatic spread:

favored by carcinoma (Malignant epithelium).

- Breast carcinoma: metastasis to axillary lymph nodes
- Lung carcinomas: metastasis to bronchial lymph nodes.

hematogenous spread:

- Hematogenous spread is favored by sarcomas (Malignant mesenchymal) but can also occur in carcinomas.
- Veins are more commonly invaded.
- The liver and lungs are the most frequently involved secondary sites.

seeding of the body cavities:

- Spread by seeding occurs when neoplasms invade a natural body cavity such as: Pleural and peritoneal cavity.
- This mode of dissemination is particularly characteristic of cancers of the ovary, which often cover the peritoneal surfaces widely.

Dysplasia

Definition:

loss in the uniformity of the individual cells and a loss in their architectural orientation.

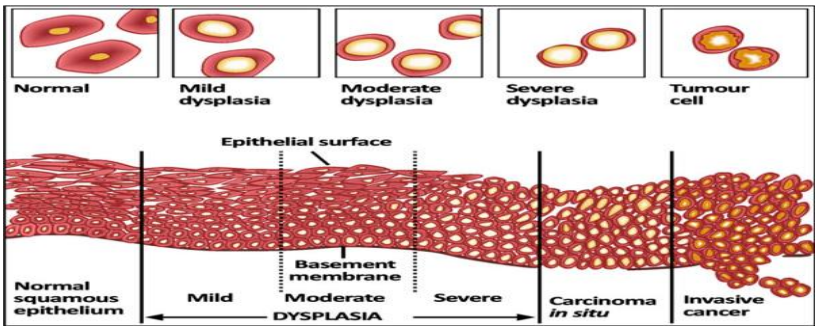
Characteristics:

- It is a non-neoplastic process but a premalignant condition(precancer).
- It occurs mainly in the epithelia (**never** seen in mesenchymal) .
- Dysplastic cells show a degree of: pleomorphism, increase in nuclear/cell ratio (because of the enlarged nucleus) , hyperchrmasia, irregular nuclei, increased mitoses, loss of polarity & a disordered maturation or total failure of maturation.
- does not necessarily progress to cancer.
- may be reversible.

Risk of cancer:

The risk of invasive cancer varies with:

- grade of dysplasia (mild, moderate, severe).
- duration of dysplasia.
- site of dysplasia : dysplasia in cervix can be reversible ,but in endometrium is NOT.



Differences between dysplasia & cancer:

- Lack of invasiveness.
- Reversibility.

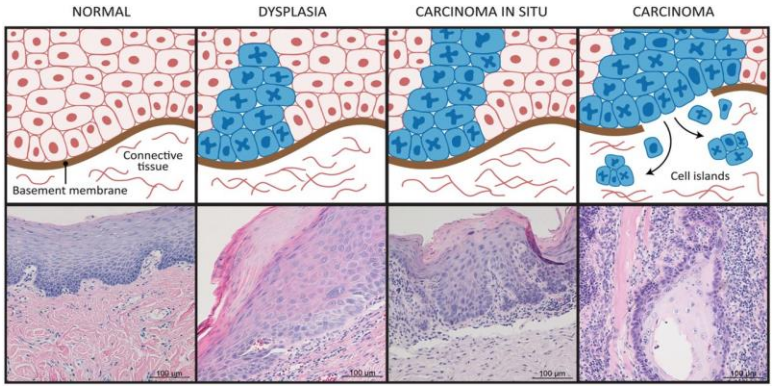
Carcinoma in-Situ

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.

- It is applicable only to epithelial neoplasms
- carcinoma in situ is irreversible.
- It is true neoplasm except invasiveness.
- It displays the cytological features of malignancy without invading the basement membrane.
- Carcinoma in situ is severe dysplasia .



Summary:

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.

What is Carcinogenesis?

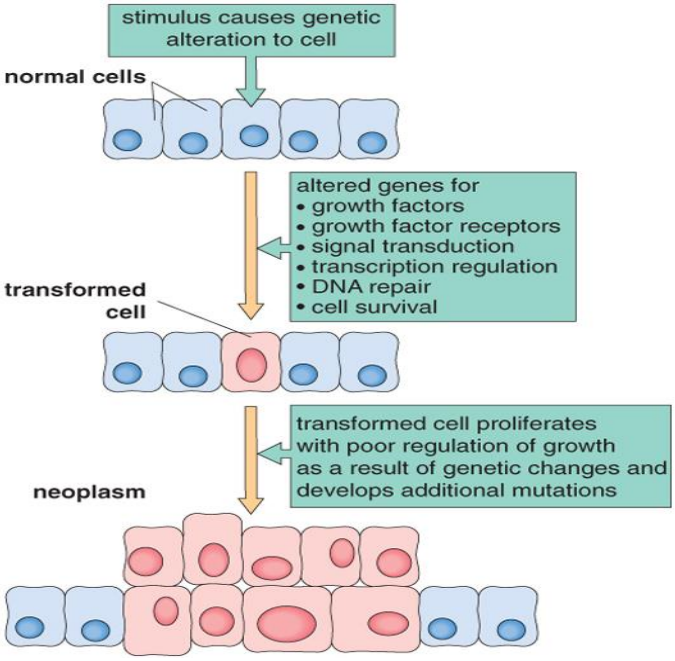
- is a multistep process at both the genetic and the phenotypic levels.

Another definition: the initiation of cancer formation.

it can be Environmental or Inhereted.

Environmental:

1- Chemical
2- Radiation
3- infections



It starts with a genetic damage.

Genetic damage lead to " mutation"

single cell which has the genetic damage undergoes neoplastic proliferation forming the tumor mass.

Neoplastic proliferation is characterized by poor regulation of growth, which lead to a process called 'tumor progression' : the development of new mutations.

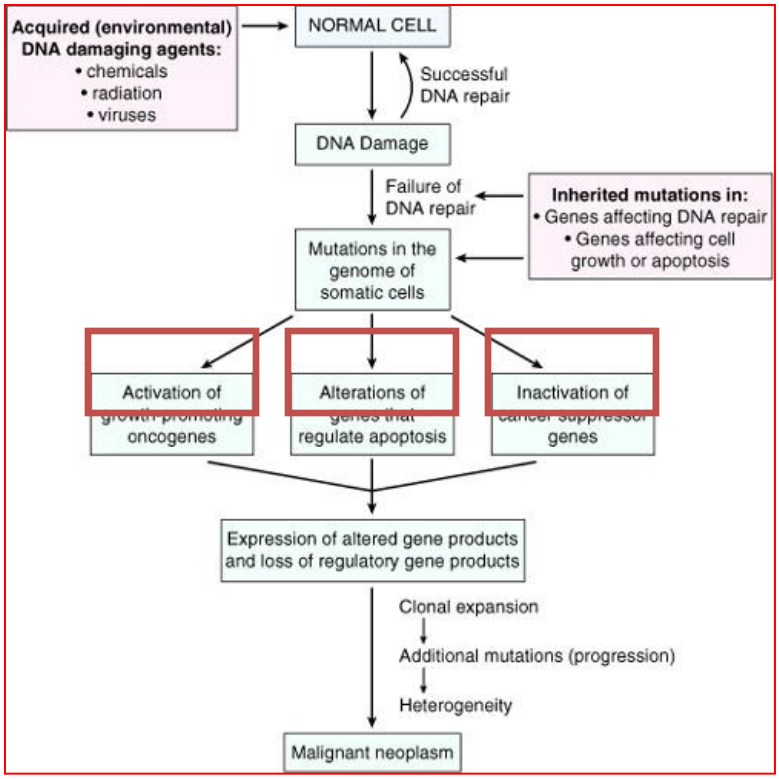
Where are the targets of the genetic damage?

- Four regulatory genes are the main targets:

1- Growth promoting protooncogenes.

Protooncogene > mutation > oncogene.

2- Growth inhibiting (supressors) genes
3- Genes regulating apoptosis
4- DNA repair genes



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

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

كل هذه المحاضرة ندرس الخمس تغيرات هذه بالتفصيل >

1- Self-sufficiency in Growth signals:

Oncogene: Gene that promote autonomous cell growth (نمو الخلايا المستقل) in cancer cells.

or a gene that in certain circumstances can transform a cell into a tumor cell.

They are derived by mutations in protooncogenes , They are characterized by the ability to promote cell growth in the absence of normal growth-promoting signals.

Oncoprotein is the product.

extra: a protein that is coded for by a viral oncogene which has been integrated into the genome of a eukaryotic cell and that is involved in the regulation or synthesis of proteins linked to tumorigenic cell growth.

Protooncogenes:These genes code for proteins that help regulate cell growth. These important genes are called proto-oncogenes.
A change in the DNA sequence (when mutation happen) of the proto-oncogene gives rise to an oncogene, which produces a different protein(Oncoprotein) that interferes with normal cell regulation.

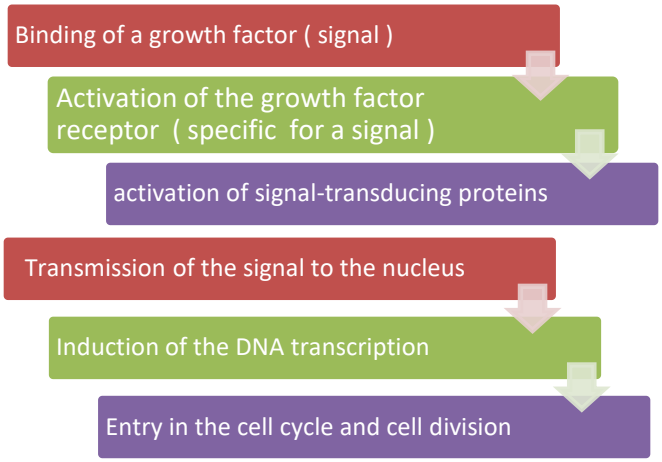
إذا حدثت طفرة ممكن تسبب تغير في أحد هذه المراحل فبالتالي راح يكون فيه
Self-sufficiency in growth signals

والصفحات الجاية تتكلم عن كل مرحلة كيف تتغير إذا حدثت فيها الطفرة:

Oncoprotein: من أمثلة البروتينات اللي ممكن تكون بروتينات ورمية

- growth factor (signal)
- receptors on cell membrane
- signal-transducing proteins
- any protein synthased by a gene

cell cycle of growth factor:



* this is the normal mechanism for a growth signal transmission in a cell.

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.
E.g.
Sarcomas(Malignant neoplasms arising in mesenchymal tissues) ---- >TGF-a
Glioblastoma(brain tumors) ----->PDGF

2-Growth factors receptors:
A- mutation in the Receptors leads to continous signals to cells and uncontrolled growth.
B- over expression of the Receptors then the cells become very sensitive, hyper responsive to normal levels of growth factors.

ex:
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.

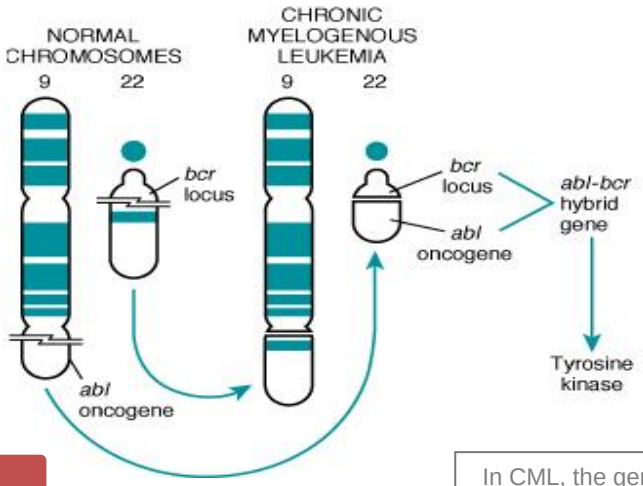
Extra: The HER2 gene makes HER2 proteins. HER2 proteins are receptors on breast cells. Normally, HER2 receptors help control how a healthy breast cell grows, divides, and repairs itself. But in about 25% of breast cancers, the HER2 gene doesn't work correctly and makes too many copies of itself (known as HER2 gene amplification). All these extra HER2 genes tell breast cells to make too many HER2 receptors (HER2 protein overexpression). This makes breast cells grow and divide in an uncontrolled way.

- 3- Signal-transducing proteins:
  They receive signals from activated growth factors receptors and transmitte them to the nucleus.
  Examples :

  A- RAS:
  Mutations in RAS the cells will continue to proliferate, 30% of all human tumors contain mutated RAS gene. E.g: 1-colon 2- Pancreas cancers.
  Mutations of the RAS gene is the most common oncogene abnormality in human tumors.

  B- ABL gene:
  protooncogene has a tyrosine kinase
  A tyrosine kinase is an enzyme that can a phosphate group from ATP to a protein
  It functions as an "on" or "off" switch in cellular functions.
  activity is controlled by negative regulatory mechanism.

  ABL
  activity.
  transfer
  in a cell.
  many
  Its



  E.g: chronic myeloid leukemia CML

  t(9,22) ---ABL gene transferred from ch. 9 to ch. 22

  Fusion with BCR ---> BCR-ABL

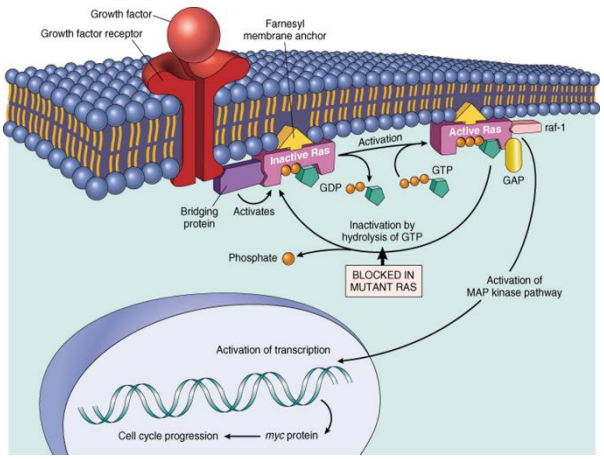
  BCR-ABL has tyrosine kinase acttivity ---(oncogenec)

  In CML, the gene (ABL) is activated by being translocated from chromosome 9 within the BCR (breakpoint cluster region) gene on chromosome 22. This new fusion gene, *BCR-ABL*, encodes an unregulated, cytoplasm-targeted tyrosine kinase that allows the cells to proliferate without being regulated by cytokines. This, in turn, allows the cell to become cancerous.

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

  helpful vid click here.

4- Nuclear transcription factors:
Mutations may affect genes that regulate transcription of DNA >growth autonomy.



E.g. MYC:
MYC protooncogene produce MYC protein when cell receives growth signals, it binds to DNA leading to activation of growth-related genes.

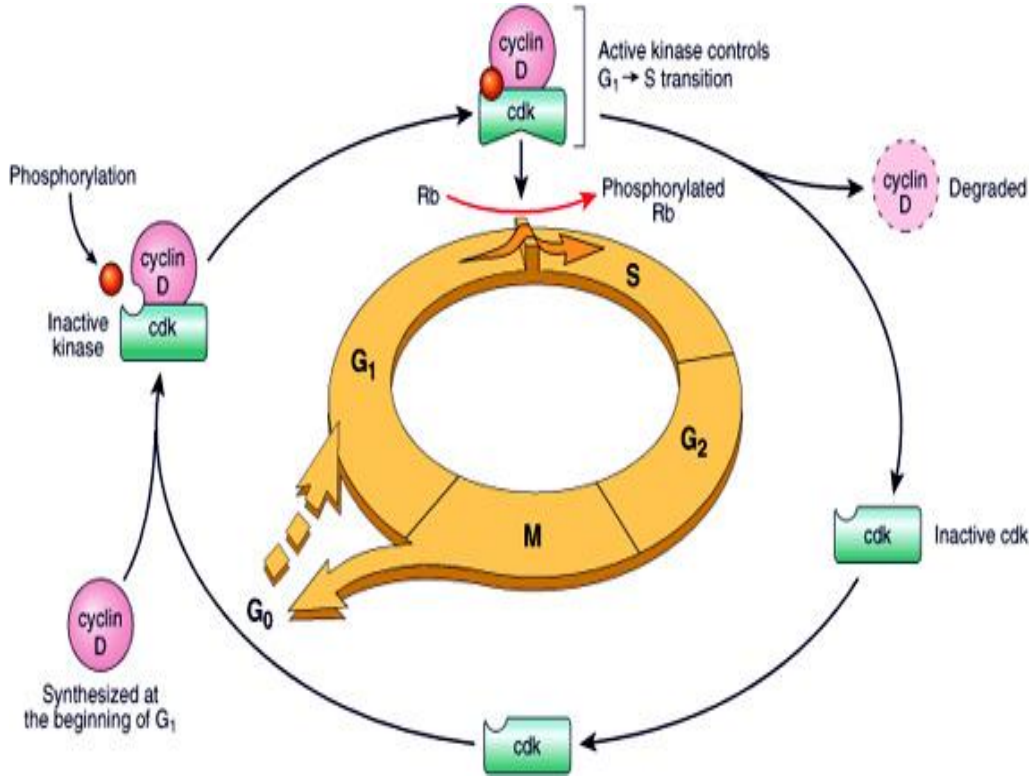
Normally MYC decreases when cell cycle begins **but** in tumors there is sustained expression of MYC leads to continuous proliferation.

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.

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

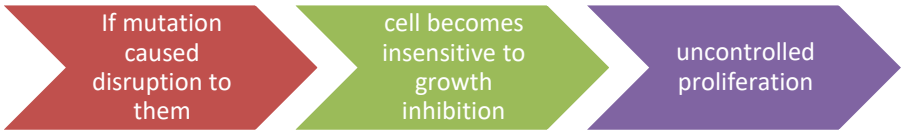
CDK4 is amplified in melanoma(skin cancer) and sarcomas.

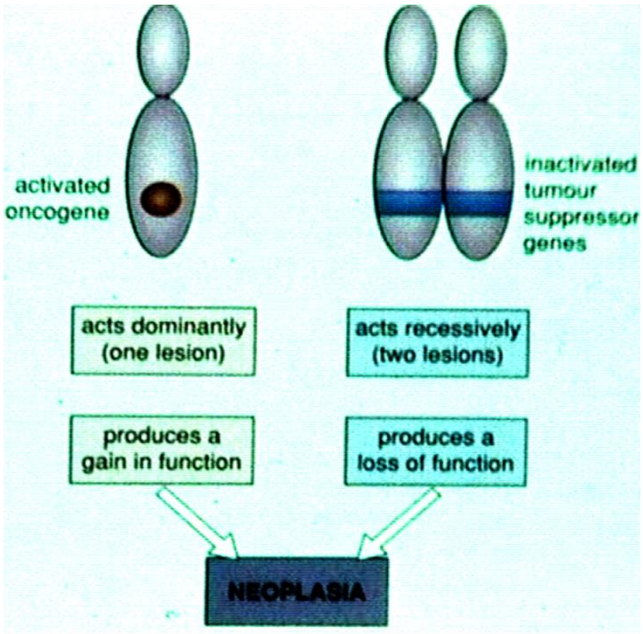


2-Insensitivity to growth-inhibitory signals:

هذا التغير بيكون بسبب طفرة في جين مسؤول عن التحكم في دورة حياة الخلية عن طريق **توقيفها** عند الحاجة ، أما التغير الذي قبله فكان في جين من الجينات المسؤولة عن مرحلة من مراحل دخول القروث فاكتورز.

Tumor suppressor genes control (apply brakes) cells proliferation.





Extra:
Retinoblastoma (Rb) is a rare form of cancer that rapidly develops from the immature cells of a retina, the light-detecting tissue of the eye. It is the most common malignant cancer of the eye in children, and it is almost exclusively found in young children.

The gene mutations which lead to Insensitivity to growth-inhibitory signals act recessively, two mutation should happen for a gene, otherwise the lesion will not be present. On the other hand, to convert protooncogens to activated oncogenes as in (self-sufficiency in growth signal) one mutation will be needed only (dominant).

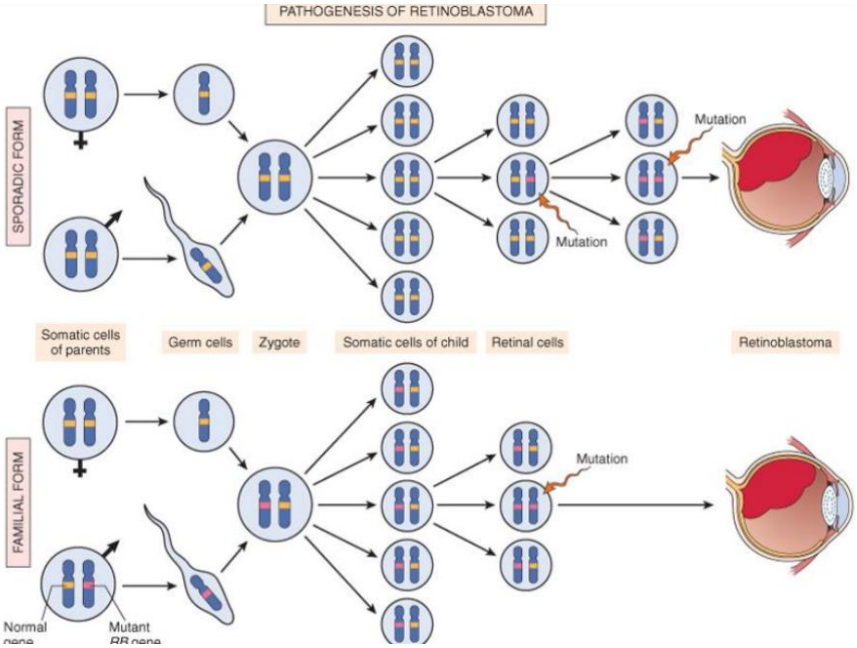
Examples : there are 4 examples :

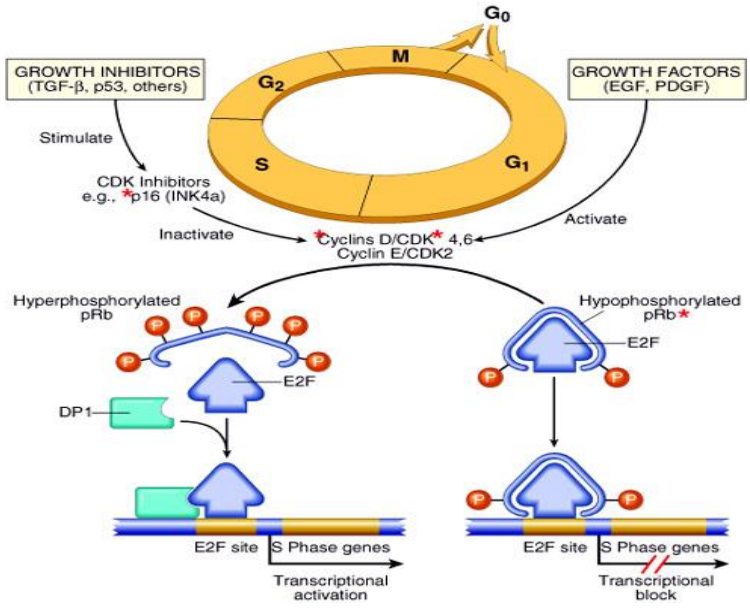
1-RB(retinoblastoma) gene: retina= شبكية العين
RB gene is a DNA-binding protein and it is located on chromosome 13
First tumor supressor gene discovered, It was discovered initially in retinoblastomas, Found in other tumorse.g. breast ca.

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, it 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


PATHOGENESIS OF RETINOBLASTOMA
SPORADIC FORM
Mutation
Mutation
Somatic cells of parents
Germ cells
Zygote
Somatic cells of child
Retinal cells
Retinoblastoma
FAMILIAL FORM
Mutation
Normal
Mutant


G0
M
G2
S
G1
GROWTH INHIBITORS (TGF-β, p53, others)
GROWTH FACTORS (EGF, PDGF)
Stimulate
CDK Inhibitors e.g., *p16 (INK4a)
Inactivate
Activate
Cyclins D/CDK 4,6
Cyclin E/CDK2
Hyperphosphorylated pRb
E2F
DP1
E2F site
S Phase genes
Transcriptional activation
Hypophosphorylated pRb*
E2F
E2F site
S Phase genes
Transcriptional block

2- TGF-b Transforming Growth Factor- b pathway:

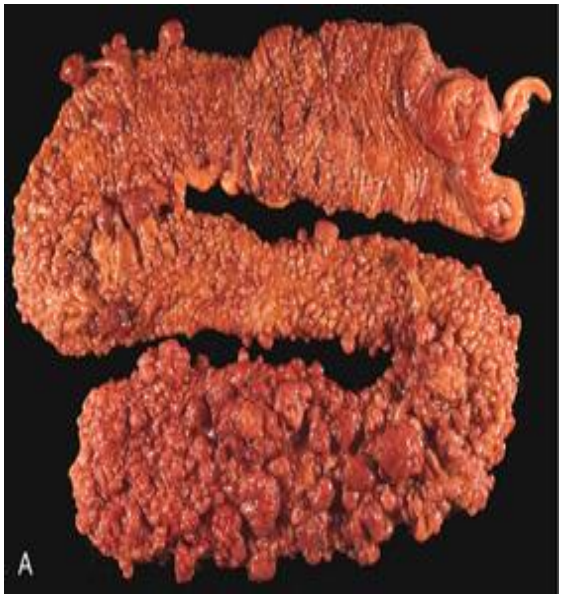
-TGF-b is active > inhibitor of proliferation
-Inactivation of TGF-b > lead to cell proliferation
*It regulates RB pathway

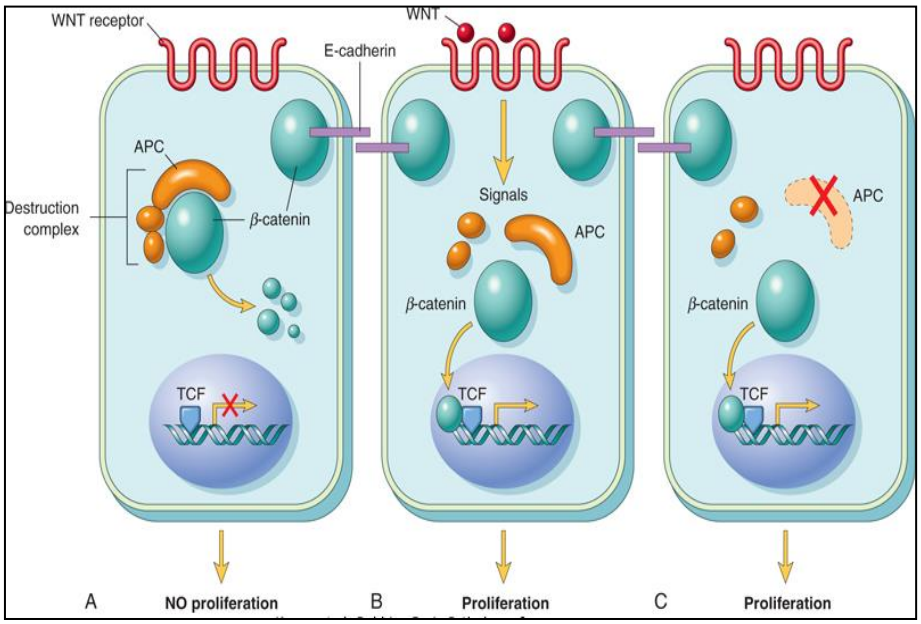
Mutations in TGF-b pathway are present in :

a) 100% of pancreatic cancers
b) 83% of colon cancers

3- APC Adenomatous Polyposis Coli – b Catenin pathway:

APC is tumor supressor gene = It has anti-proliferative action through inhibition of b-Catenin which activate cell proliferation
APC gene loss is very common in colon cancers
Individuals with mutant APC develop thousands of colonic polyps (أورام قولونية حميدة)
One or more of the polyps will progress to colonic carcinoma (تصبح خبيثة)
APC mutations are seen in 70% to 80% of sporadic colon cancers



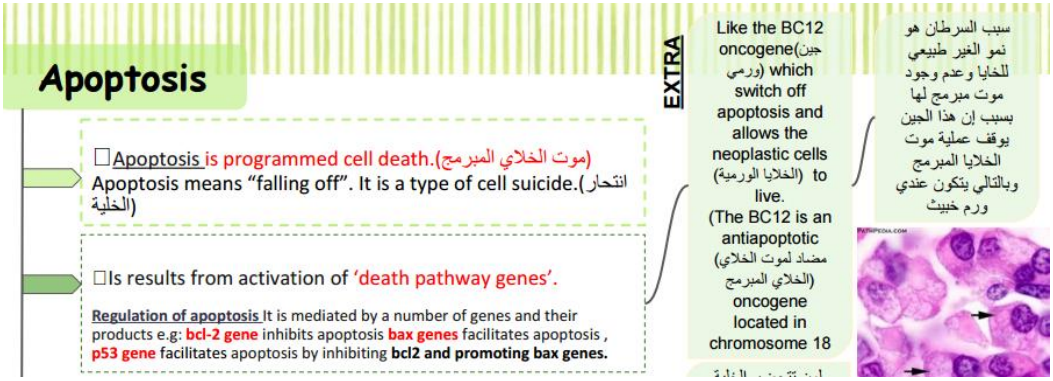


A. APC is inhibiting b-catenin pathway as there is no signal for growth. B. b- catenin pathway is activated by inhibiting APC as there is a signal for growth. C. there is no signal for growth but b- catenin is activated due to mutation in APC gene and loss of APC, as b-catenin is activated, even if there is no signal the cell will proliferate .

4- P53

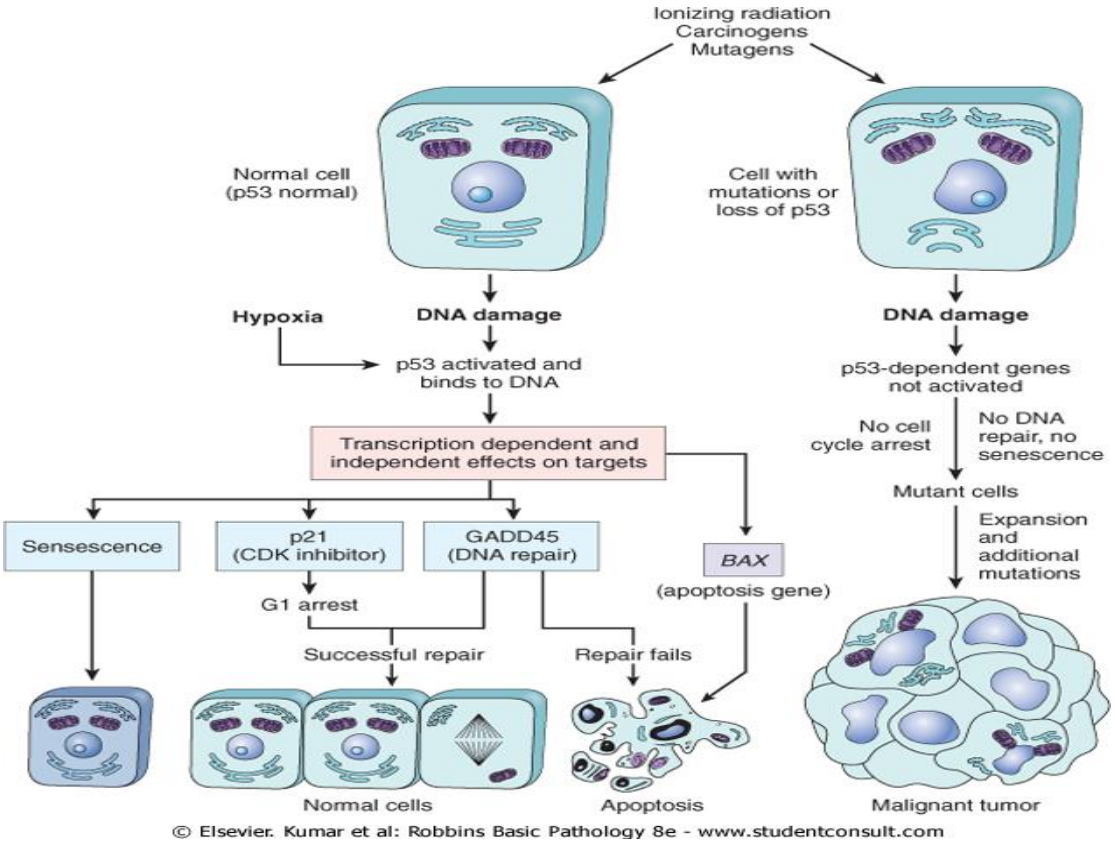
It has multiple functions Mainly :

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



TEAM 435
يربط لكم بين الابتوزز والسرطان

- 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

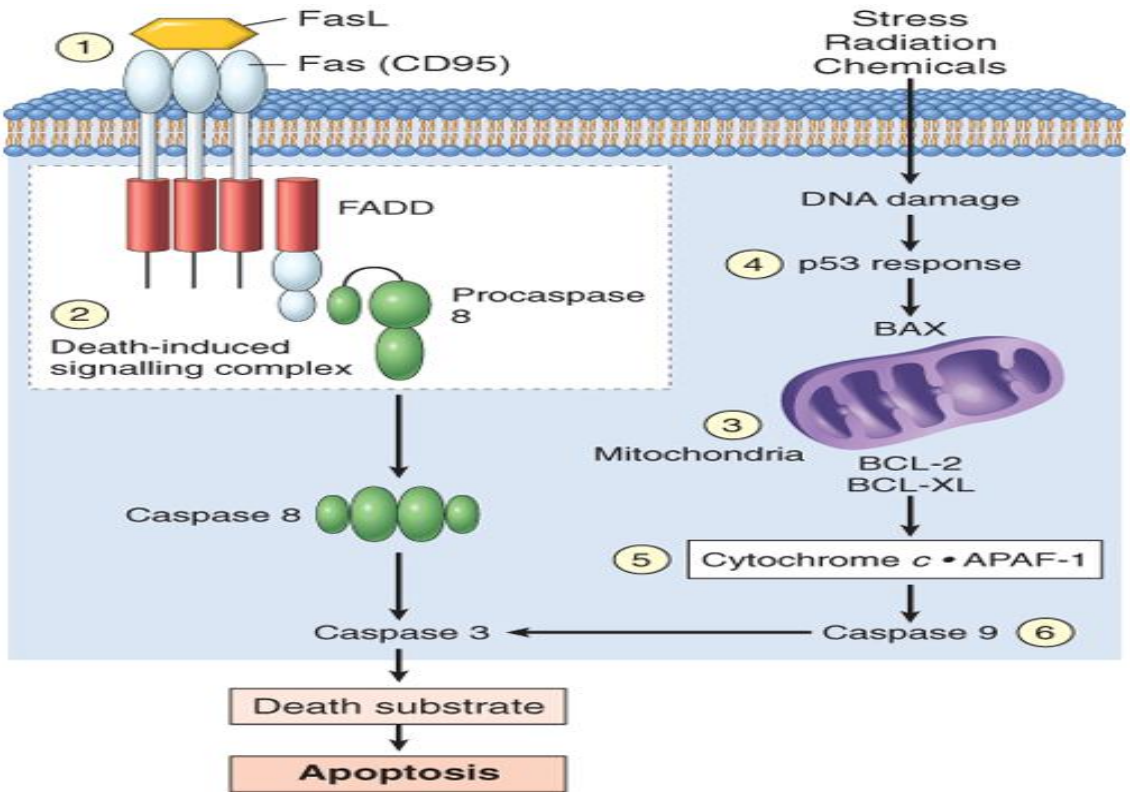


-P53 is called the “ guardian of the genome”
-70% of human cancers have a defect in P53
-It has been reported with almost all types of cancers : e.g. lung, colon, breast
-In most cases, mutations are acquired, but can be inhereted, e.g : Li-Fraumeni syndrome

3- Evasion of apoptosis:

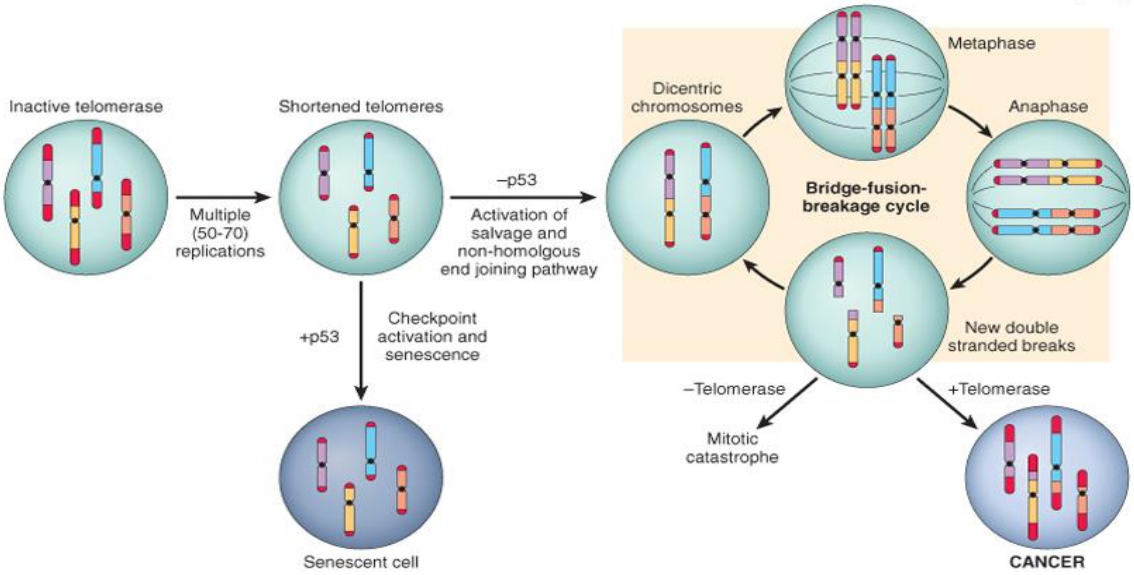
evasion = التهرب

-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



4- 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



After 50-70 times of replication Telomerase (the red one) will be short. If P53 is activated it will sense it and the cell will stop proliferation anymore or undergoes apoptosis, but if it is mutated, the cell will undergo mitosis, if it is a cancerous cell Telomerase will be active, if not the cell will eventually be dead by Mitotic catastrophe.

Further explanations about mitotic catastrophe : **Mitotic catastrophe** refers to a mechanism of delayed mitotic-linked cell death, a sequence of events resulting from premature or inappropriate entry of cells into mitosis that can be caused by chemical or physical stresses.[1] Mitotic catastrophe is unrelated to programmed cell death or apoptosis and is observed in cells lacking functional apoptotic pathways.

5- sustained angiogenesis:

-Angiogenesis is required for metastasis

-Neovascularization has two main effects:

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

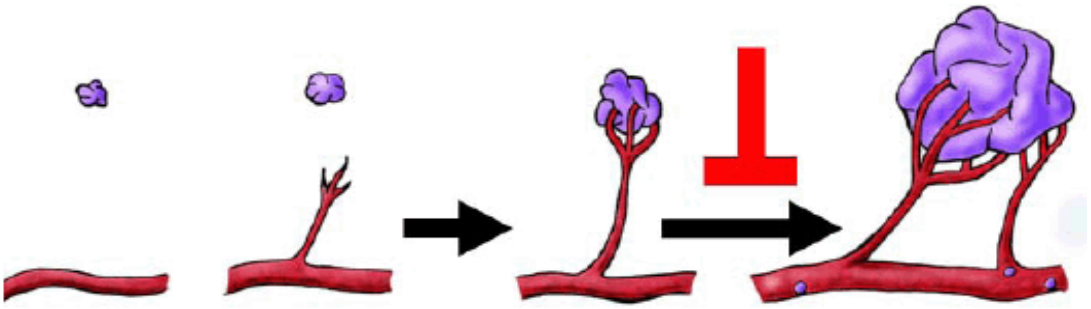
-How do tumors develop a blood supply?

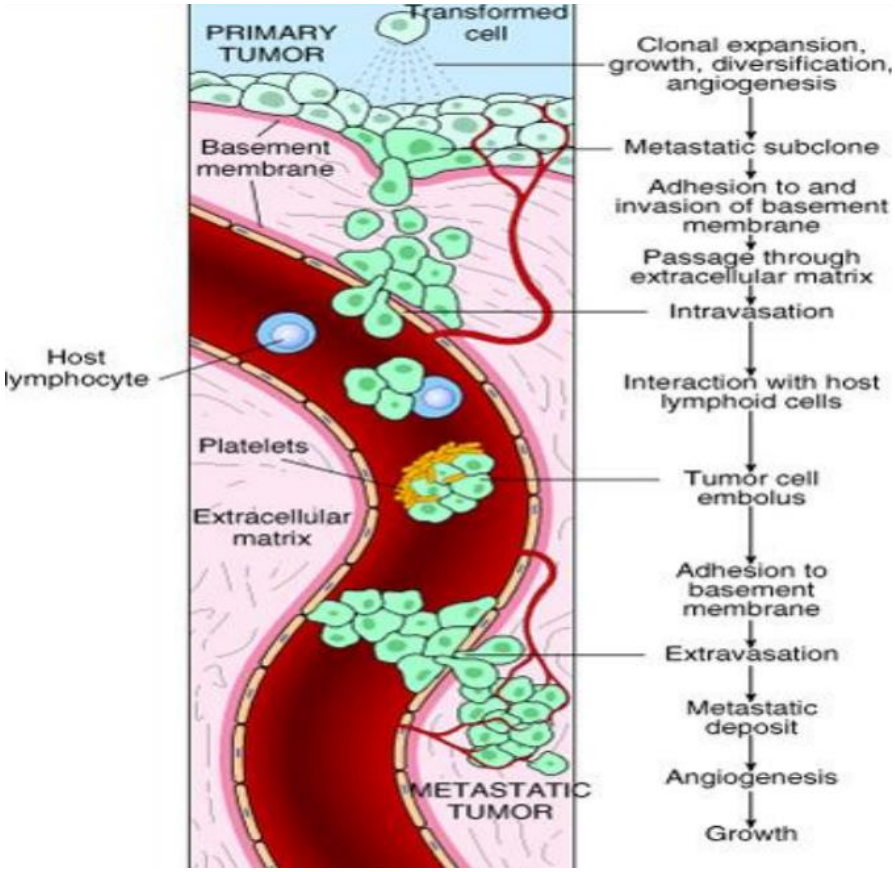
Tumor-associated angiogenic factors

These factors may be produced by tumor cells or by inflammatory cells infiltrating the tumor e.g. macrophages

Important factors :

1- Vascular endothelial growth factor(VEGF)
2- Fibroblast growth factor





6- Ability to invade and metastsize:

Two phases :

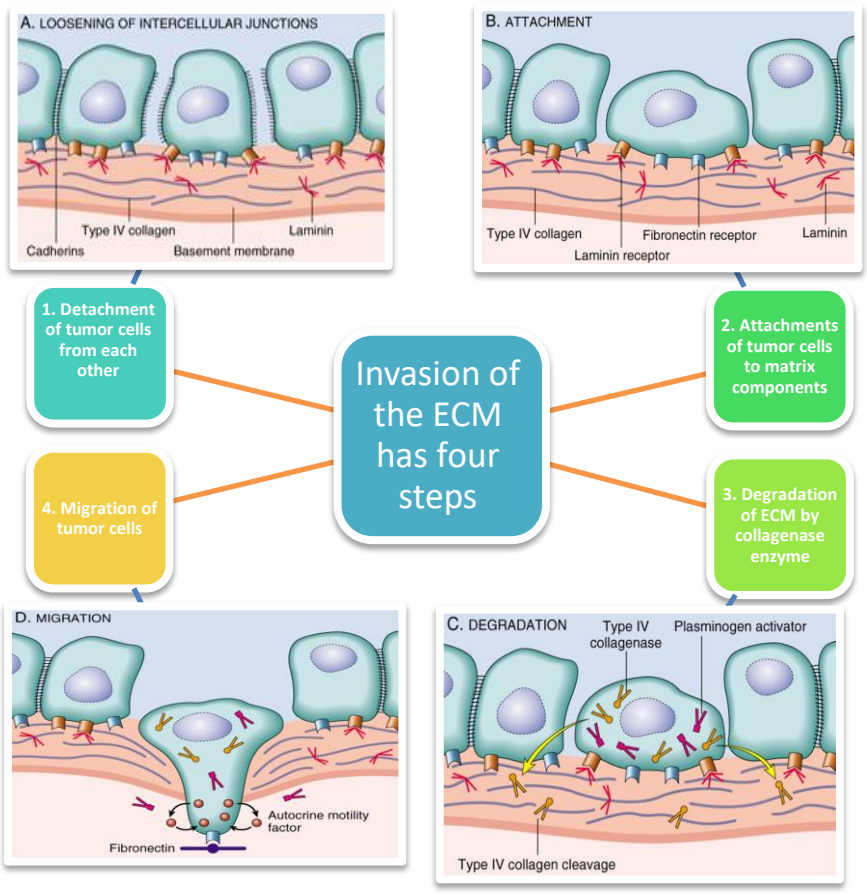
1. Invasion of extracellular matrix
2. Vascular dissimenation and homing of tumor cells

1) Invasion of ECM:

   a) Malignant cells first breach the underlying basement membrane
   b) Traverse the interstitial tissue
   c) Penetrate the vascular basement membrane
   d) Gain access to the circulation

2) Vascular dissemination and homing of tumor cells:

   a) May form emboli
   b) Most travel as single cells
   c) Adhesion to vascular endothelium
   d) Extravasation



That's the Main changes in the cell physiology that lead to formation of the malignant phenotype 🕊

Genomic Instability (عدم الاستقرار الجيني)

-Enabler of malignancy

-Due to defect in DNA repair genes

-Examples:

1- Hereditary Nonpolyposis colon carcinoma(HNPCC)

2-Xeroderma pigmentosum

3-Familial breast cancer

^Due to mutations in BRCA1 and BRCA2 genes , These genes regulate DNA repair

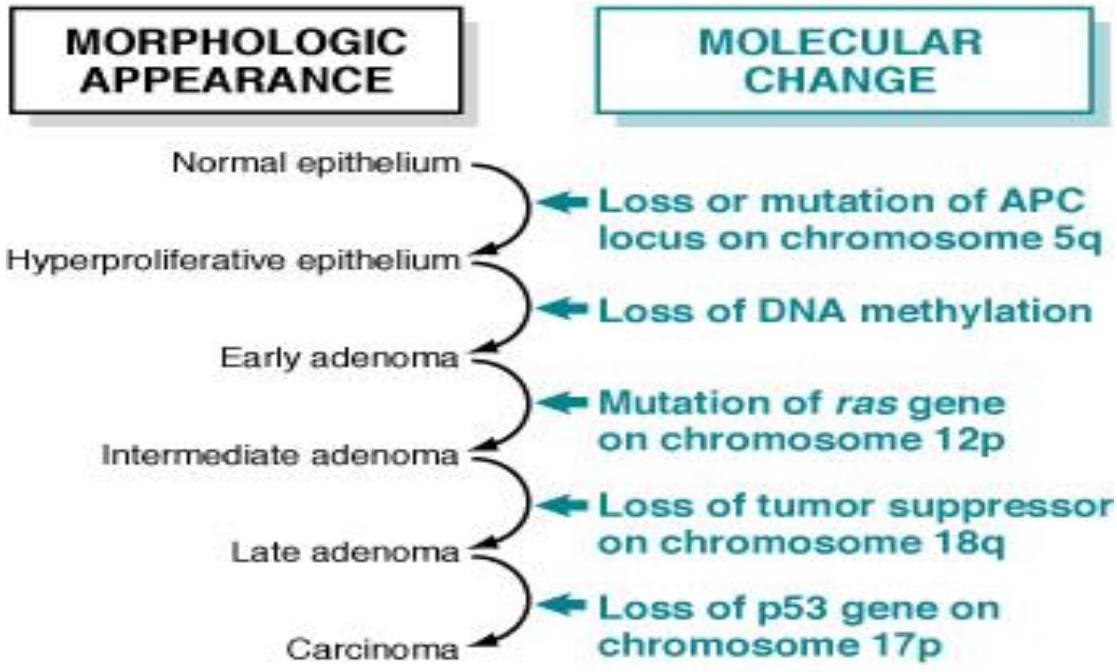
Account for 80% of familial breast cancer

They are also involved in other malignancies

Molecular Basis of multistep Carcinogenesis

-Cancer results from accumulation of multiple mutations

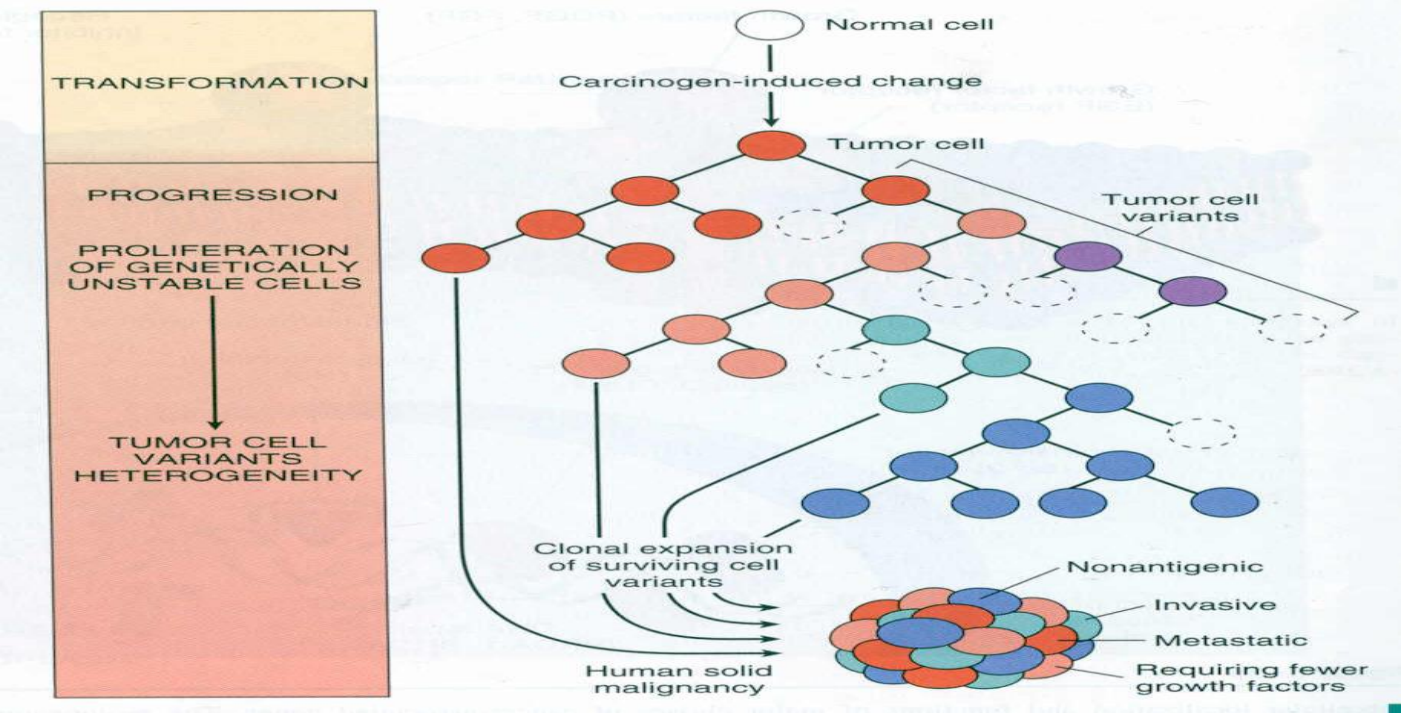
-All cancers have multiple genetic alterations, involving activation of several oncogenes and loss of two or more tumor suppressor genes



Tumor progression

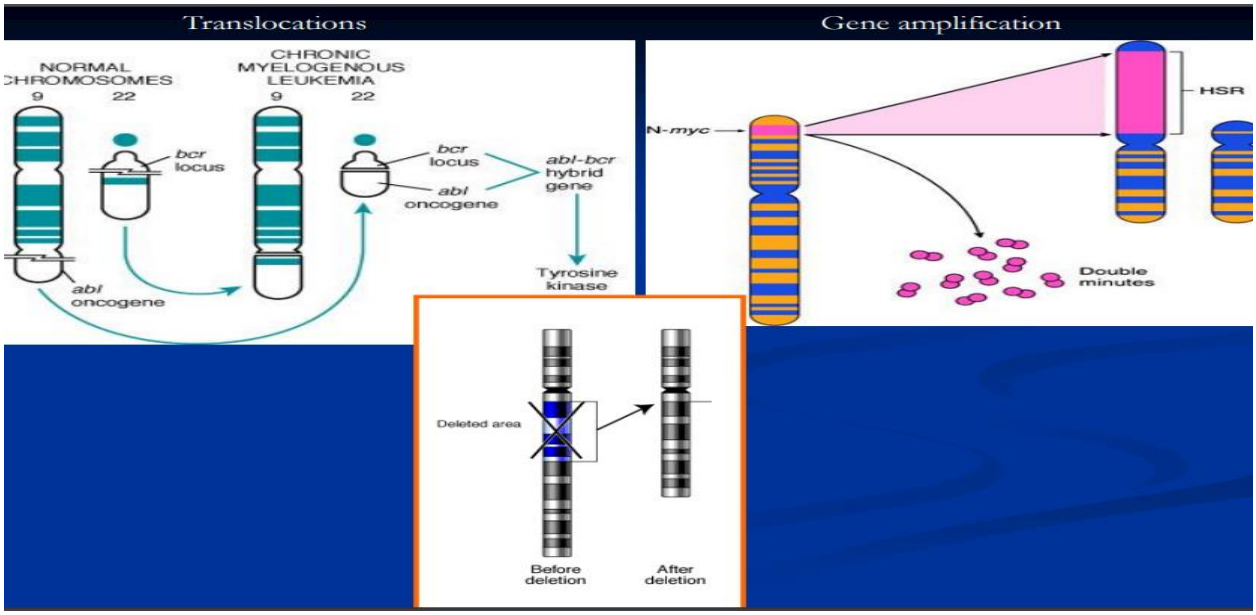
-Many tumors become more aggressive and acquire greater malignant potential…this is called “ tumor progression” …not increase in size!!

-By the time, the tumor become clinically evident, their constituent cells are extremely heterogeneous



Karyotypic Changes in Tumors

1) Translocations:
    A. In CML : t(9,22) …" Philadelphia chromosome"
    B. In Burkitt Lymphoma : t(8,14)
    C. In Follicular Lymphoma : t(14,18)
2) Deletions
3) Gene amplification:
    A. 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	

ETIOLOGY OF CANCER:
CARCINOGENIC AGENTS

Epidemiology (Prevalence)

- Will help to discover aetiology.
- Planning of preventive measures.
- To know what is common and what is rare.
- Development of screening methods for early diagnosis.

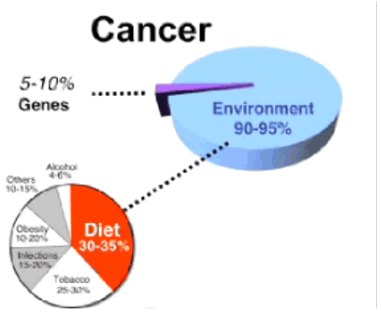
Factors affecting incidence of cancer:

1- Geographic and Environmental factors:

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

2- Environmental factors:

a- Asbestos (mineral): mesothelioma. < Malignant
b- Smoking: lung cancer.
c-Multiple sexual partners: cervical cancer = (uterine cervical carcinoma).
d- Fatty diets: colonic cancer.

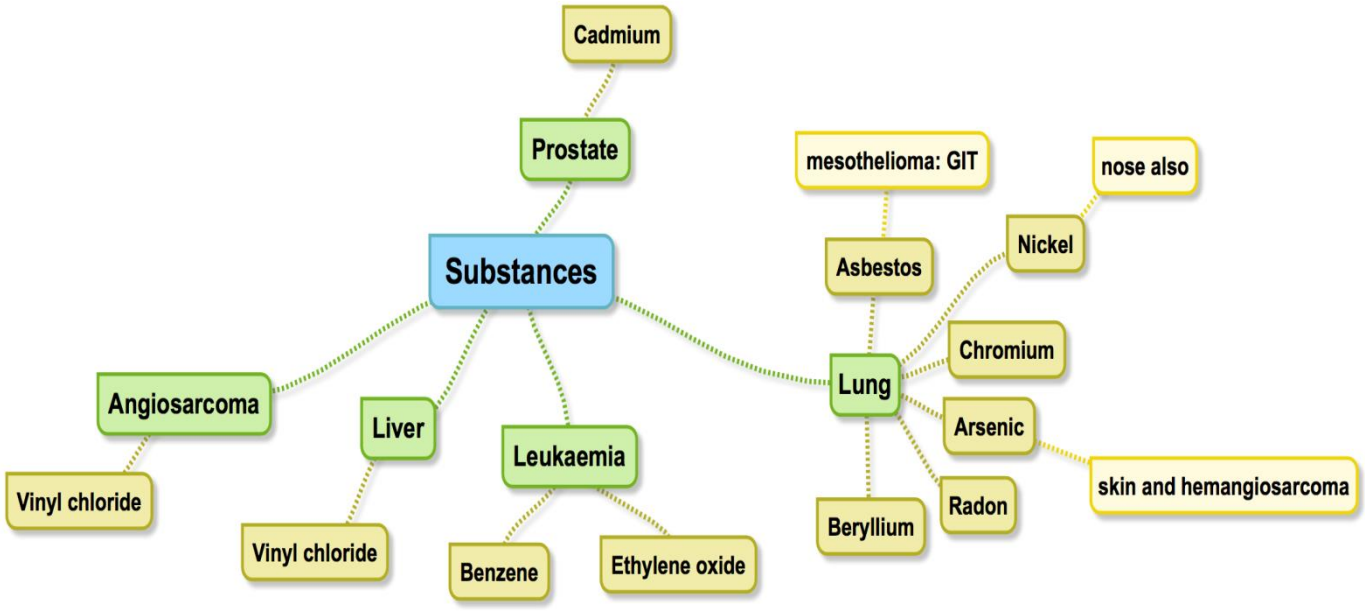


Agent/Group of Agents	Human Cancer Site and Type for Which Reasonable Evidence Is Available	Typical Use/Occurrence
Arsenic and arsenic compounds	Lung, skin, hemangiosarcoma	Byproduct of metal smelting Component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and 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

**important

Summary

3-



Age:

a- Generally, the frequency of cancer increases with age.
b-Most cancer mortality occurs between 55 and 75.
c-Cancer mortality is also increased during childhood. (less than 10 years old)
d-Most common tumours of children: Leukemia (most common), tumors of CNS (most common solid), Lymphomas, soft tissue and bone sarcomas.

4-Heredity Factors:

a-Autosomal dominant cancer syndromes

- Several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor.

-E.g. Retinoblastoma in children:

- 40% of Retinoblastomas are familial.

-carriers of the gene have 10000 fold increase in the risk of developing Retinoblastoma.

-E.g. multiple endocrine neoplasia (MEN syndrome).

- certain mutations
- Mode of inheritance: Autosomal dominant.
- The carrier has very risk in developing a tumor depending on the mutated gene.

b- Autosomal Recessive Syndromes of Defective DNA repair.

- A group of rare autosomal recessive disorders is collectively characterized **by chromosomal or DNA instability and high rates of certain cancers.**

- **e.g. xeroderma pigmentosum.**

-Small group of autosomal recessive disorders.

-Characterized by DNA instability.

c- Familial Cancers. (uncertain inheritance).

- All the common types of cancers that occur sporadically have been reported to occur in familial forms where the pattern of inheritance is unclear.

- E.g. breast, colon, ovary, brain.

- Familial cancers usually have unique features:

-Start at early age.

-Multiple or bilateral. (two organs: breast and ovaries)

-Two or more relatives.

Autosomal Dominant Cancer Syndromes	
Gene(s)	**Inherited Predisposition**
RB	Retinoblastoma
TP53	Li-Fraumeni syndrome (various tumors)
p16INK4A	Melanoma
APC	Familial adenomatous polyposis/colon cancer
NF1, NF2	Neurofibromatosis I and 2
BRCA1, BRCA2	Breast and ovarian tumors
MEN1, RET	Multiple endocrine neoplasia I and 2
MSH2, MLH1, MSH6	Hereditary nonpolyposis colon cancer
PATCH	Nevoid basal cell carcinoma syndrome
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum Ataxia-telangiectasia Bloom syndrome Fanconi anemia	
Familial Cancers of Uncertain Inheritance	
Breast cancer (not linked to *BRCA1* or *BRCA2*) Ovarian cancer Pancreatic cancer	

**the table is important

5-Aquired pre-neoplastic disorders: (Some Clinical conditions that predispose to cancer) (dysplasia)

a-Dysplastic bronchial mucosa in smokers >>>>> lung carcinoma.

b-Liver cirrhosis (caused by alcohol or hepatitis B virus). >>>>> liver cell carcinoma.

c-Margins of chronic skin fistula >>>>> squamous cell carcinoma.

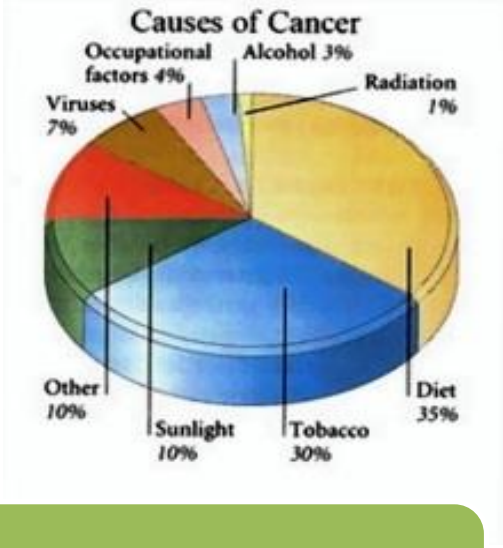
d- Endometrial hyperplasia (in endometrial we don't use dysplasia) >>>> endometrial carcinoma.

e- Leukoplakia of the oral cavity, vulva or penis >>>> squamous cell carcinoma.

f- Villous adenoma of the colon or rectum >>>> colorectal adenocarcinoma.

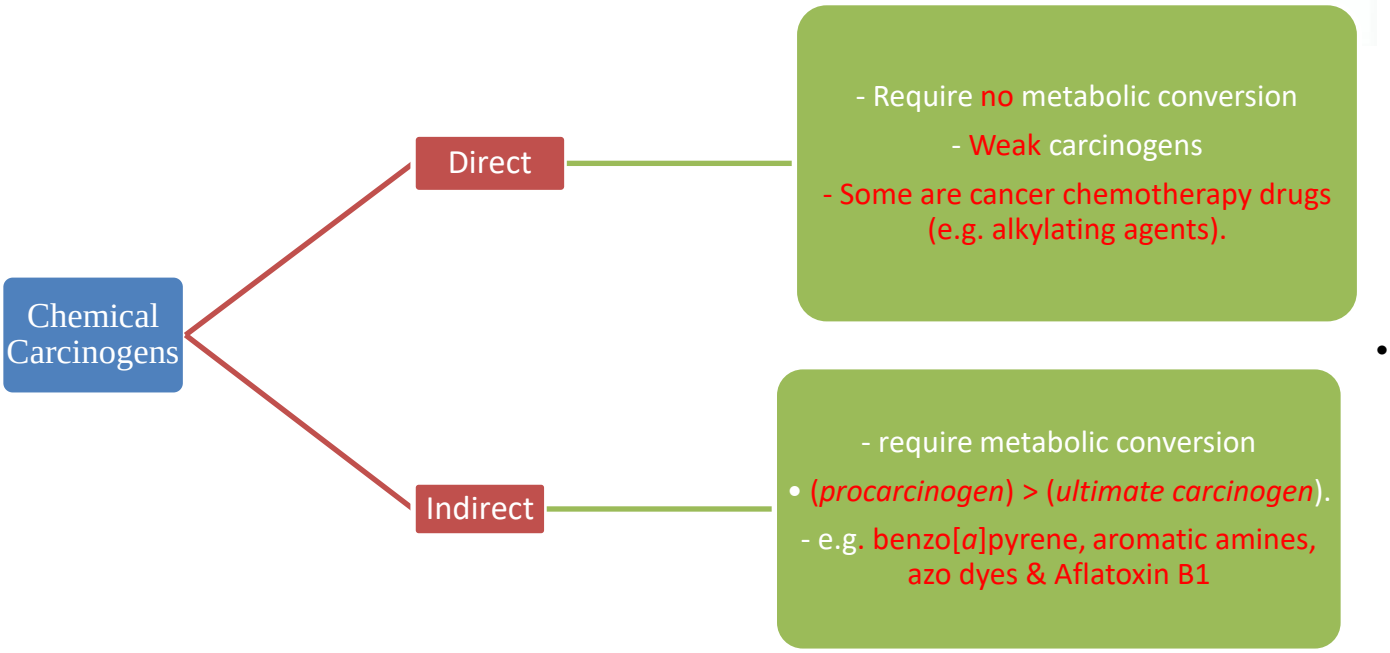
Carcinogenic Agents: (aetiology)

1-Chemicals.
2-Radiation.
3- Microbial agents. (infectious agents including viruses and microbes)



1-Chemical Carcinogens:

- **Natural or synthetic.**
- **Direct reacting or indirect:**



Mechanisms of action:

- Most chemical carcinogens are mutagenic i.e. cause genetic
- mutations.
- the commonly mutated oncogenes & tumour 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.

Examples:

- Alkylating agents.
- Polycyclic hydrocarbons:

- Cigarette smoking
- Animal fats during broiling meats
- Smoked meats and fish

- Aromatic amines and azo dyes:

- **B-naphthylamine cause bladder cancer = (transitional cell carcinoma) in rubber industries and aniline dye.**
- **Some azo dyes are used to colour food also can cause bladder cancer.**

Other substances:

- **Nitrosamines and nitrosamides are used as preservatives they cause gastric cancer.**
- **Aflatoxin B1: produced by Aspergillus fungus growing on improperly stored grains. It causes hepatocellular carcinoma.**

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

****Important**

2-Radiation Carcinogenesis (causes all types of mutations):

Radiation, whatever its source:

- UV rays of sunlight
- x-rays
- nuclear fission
- radionuclides

it is an established carcinogen.

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 to damage DNA.**
- **With extensive exposure to sunlight, the repair system is overwhelmed >> skin cancer.**
- **They cause mutations in P53 gene.**

3- viral Carcinogenesis:

Viral and Microbial oncogenesis:

- **DNA viruses**
- **RNA viruses**
- **other organisms e.g. H. Pylori bacteria**

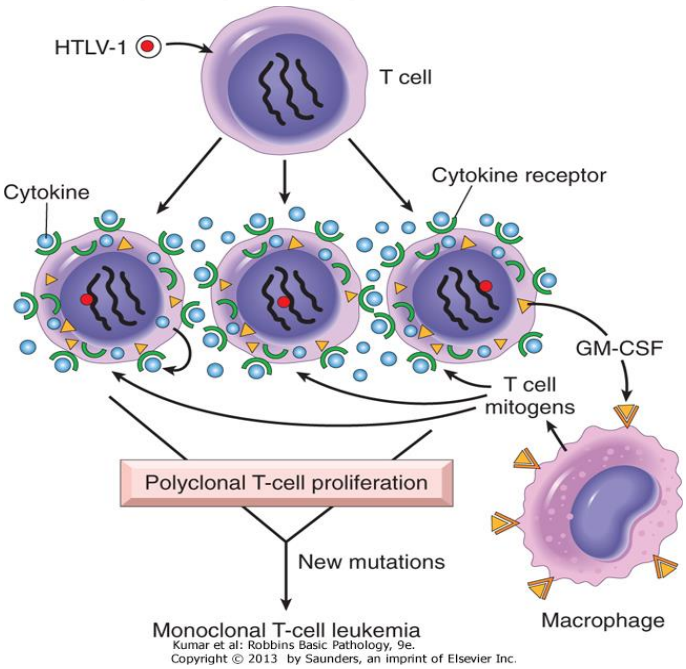
- carry genes that induce cell replication as part of the viral life cycle.
- host cell has endogenous genes that maintain the normal cell-cycle.
- Oncogene viruses induce cellular proliferation, mimic or block cellular signals necessary for the cell cycle regulation.

***oncogenes: viruses that cause tumor.**

RNA Oncogenic viruses

Human T-Cell lymphotropic Virus type 1 (HTLV-1)

- **RNA retrovirus infects / transforms T-cells.**
- **causes T-Cell leukaemia/Lymphoma.**
- **Endemic in Japan and Caribbean.**
- **Transmitted like HIV (blood and sexual relationships) but only 1% of infected develop T-Cell leukaemia/Lymphoma.**
- **Prolonged latent period (20-30 years).**
- **No cure or vaccine.**
- **Treatment: chemotherapy with common relapse.**



DNA Oncogenic Viruses: (more important than RNA)

DNA viruses form stable associations with hosts DNA, thus the transcribed viral DNA transforms the host cells. (transfer to neoplastic cells)

Examples:

- **Human papilloma virus (HPV)**
- **Epstein Barr virus (EBV)**
- **Hepatitis B virus (HBV)**
- **Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8**
- **[HHV-8]) (HIV patients or patients with immunological problems)**

Human Papillomavirus (HPV): (HPV infection)

- **70 types serotypes.**
- **sexually transmitted.**
- **It causes benign warts.**
- **It causes squamous cell carcinoma of:**

➢ Cervix.
➢ Anogenital region.
➢ Mouth.
➢ Larynx.

- **HPV type 6 and 11 causes: Genital warts. (benign)**
- **HPV type 16, 18, 31: (malignant)**

1) Causes 85% of cervical carcinoma by **16 or 18.** Also causes adenocarcinoma **.**

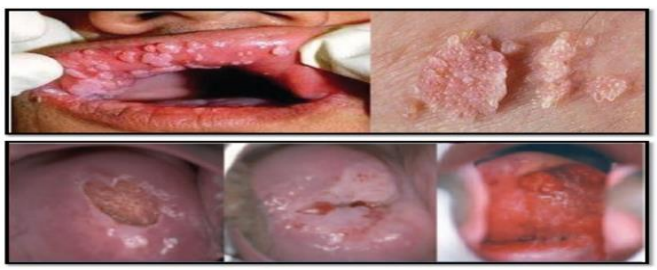
2) High risk that the virus integrates with the host's DNA.

- **over-expression of Exon 6 and 7:**

• The oncogenic potential of HPV 16 and 18 can be related to products of two early viral genes, E6 and E7.
• 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. (replaces normal transcription factors + decreases Rb synthesis).
• E7 protein binds to p53 & facilitates its degradation. (P53: gatekeeper of the cell cycle)

- **HPV infection alone is not sufficient to cause carcinoma and other factors also contribute to the development of cervical carcinoma, such as:**

➢ cigarette smoking
➢ coexisting infections
➢ hormonal changes



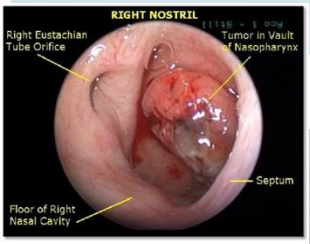
Epstein-Barr Virus:

- **EBV infection:**
- common virus worldwide
- Infects B lymphocytes and epithelial cells of nasopharynx
- causes infectious mononucleosis
- EBV infection may cause malignancy
  - Burkitt's Lymphoma (malignant)
  - B cell lymphoma in immunosuppressed
  - Nasopharyngeal carcinoma (malignant)

Epstein-Barr Virus related

Nasopharyngeal carcinoma

- Arising from nasopharygeal epithelium
- Endemic in South China and parts of Africa
- 100% of tumors contain EBV genome in endemic areas

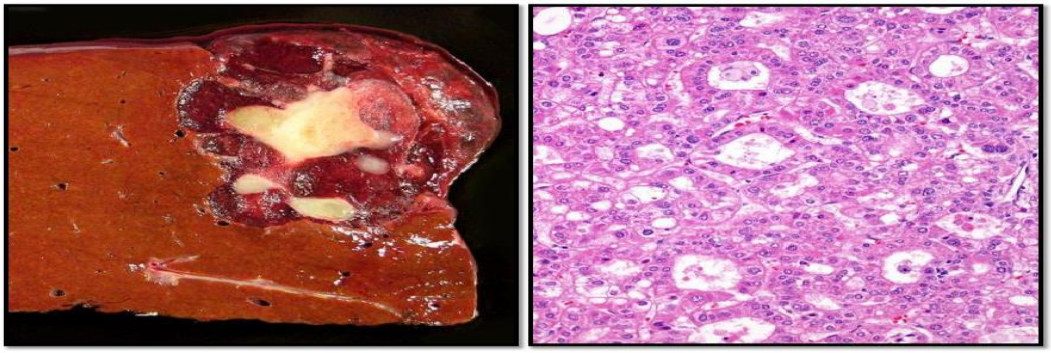


Burkitt's Lymphoma

- highly malignant B cell tumor
- sporadic rare occurrence worldwide
- most common childhood tumor in Africa
- all cases have t(8:14)
- causes B lymphocyte cell proliferation
- loss of growth regulation
- predisposes the cell to mutation, esp. t(8:14)

Hepatitis B virus (HBV)

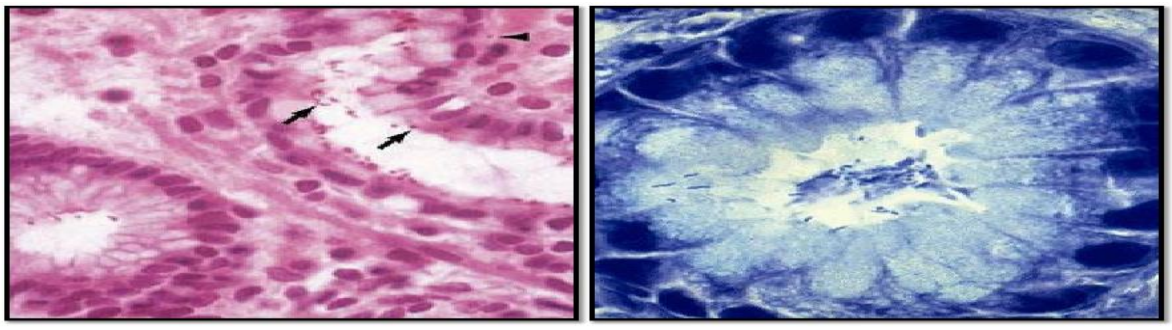
- **Strong association with Liver cell carcinoma (HCC).**
- **World-wide, but most common in Far East and Africa.**
- **HBV infection incurs up to 200-fold risk.**



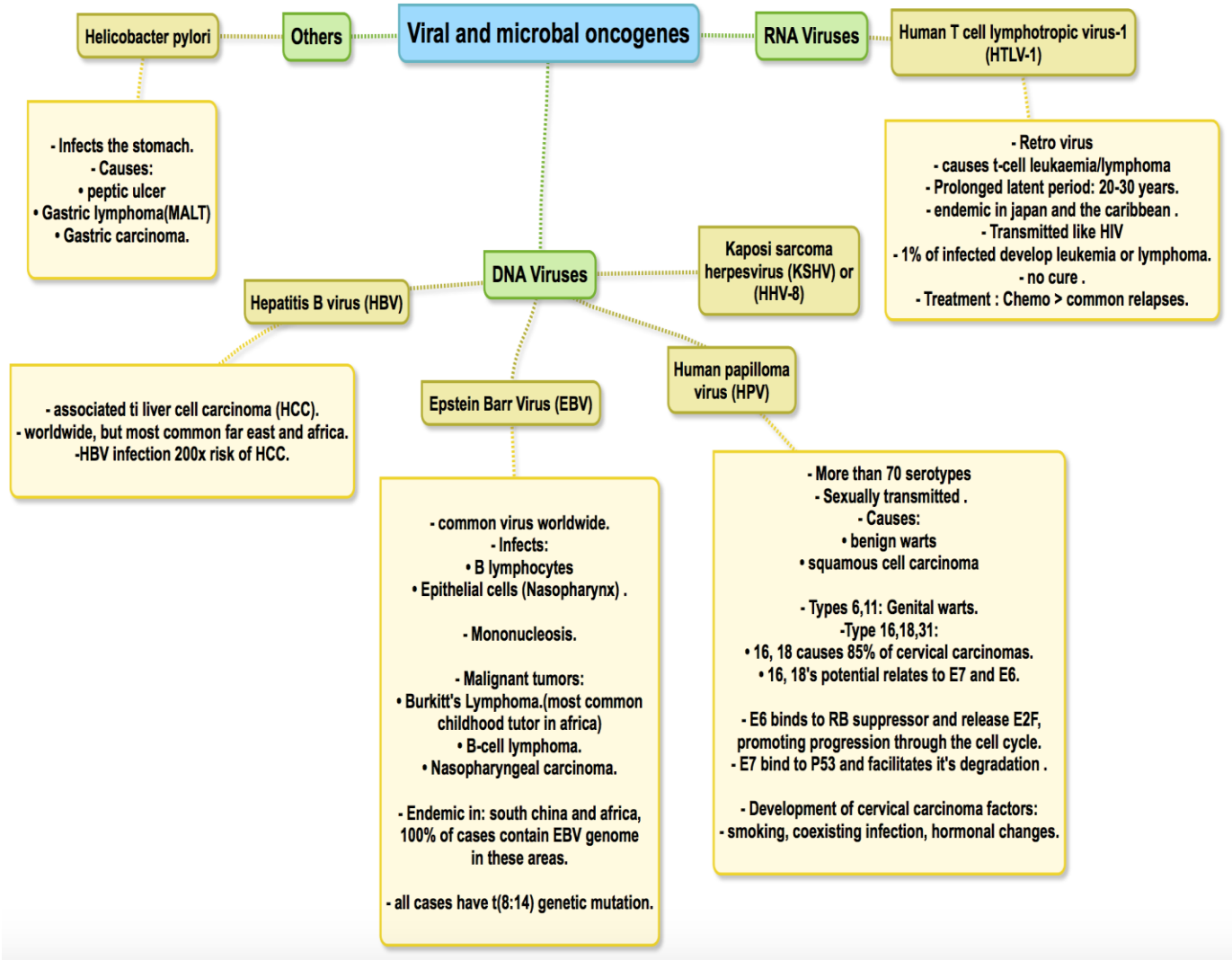
Others:

Helicobacter Pylori bacteria:

- **bacteria infecting stomach**
- **implicated in: (causes)**
  - peptic ulcers
  - gastric lymphoma
  - Mucosal Associated Lymphoid Tumor (MALT)
  - gastric carcinoma



Summary


Viral and microbal oncogenes
Others
Helicobacter pylori
- Infects the stomach.
- Causes:
• peptic ulcer
• Gastric lymphoma(MALT)
• Gastric carcinoma.
RNA Viruses
Human T cell lymphotropic virus-1 (HTLV-1)
- Retro virus
- causes t-cell leukaemia/lymphoma
- Prolonged latent period: 20-30 years.
- endemic in japan and the caribbean .
- Transmitted like HIV
- 1% of infected develop leukemia or lymphoma.
- no cure .
- Treatment : Chemo > common relapses.
DNA Viruses
Kaposi sarcoma herpesvirus (KSHV) or (HHV-8)
Hepatitis B virus (HBV)
- associated ti liver cell carcinoma (HCC).
- worldwide, but most common far east and africa.
-HBV infection 200x risk of HCC.
Epstein Barr Virus (EBV)
- common virus worldwide.
- Infects:
• B lymphocytes
• Epithelial cells (Nasopharynx) .
- Mononucleosis.
- Malignant tumors:
• Burkitt's Lymphoma.(most common childhood tutor in africa)
• B-cell lymphoma.
• Nasopharyngeal carcinoma.
- Endemic in: south china and africa, 100% of cases contain EBV genome in these areas.
- all cases have t(8:14) genetic mutation.
Human papilloma virus (HPV)
- More than 70 serotypes
- Sexually transmitted .
- Causes:
• benign warts
• squamous cell carcinoma
- Types 6,11: Genital warts.
-Type 16,18,31:
• 16, 18 causes 85% of cervical carcinomas.
• 16, 18's potential relates to E7 and E6.
- E6 binds to RB suppressor and release E2F, promoting progression through the cell cycle.
- E7 bind to P53 and facilitates it's degradation .
- Development of cervical carcinoma factors:
- smoking, coexisting infection, hormonal changes.

Summary of Eitology and tumors:

Hereditary Factors	Disease	
Autosomal Dominant Cancer Syndrome	Retinoblastoma	
	MEN Syndrome (multiple endocrine neoplasia)	
Autosomal recessive Cancer Syndrome	Xeroderma pigmentosum	DNA instability – high rates of certain cancer
Familial of uncertain cancer inheritance	Breast – Colon – Ovary – Brain pancreatic	

Etiology of Tumors	Disease
Aromatic amines (B-naphthylamine)	Bladder Cancer (transitional cell carcinoma)
Azo dyes (used to color food)	Bladder Cancer (transitional cell carcinoma)
Alfatoxin B1 (Aspergillus)in grains	Hepatocellular carcinoma
UV rays	Melanoma – squamous cell carcinoma basal cell carcinoma
HTLV-1	T-cell leukemia – lymphoma
HPV t(16-18)	Cervix carcinoma
EBV	Burkitt lymphoma (most common childhood in Africa) ,t(8,14) B-cell lymphoma Nasopharyngeal carcinoma
HBV	Liver cell carcinoma (most common in far east and Africa)
Helicobacter Pylori Bacteria	Peptic ulcer Gastric lymphoma (MALT) Gastric carcinoma
Asbestos	Mesothelioma
Multiple sexual partners	Cervical carcinoma
Fat-rich diet	Colon carcinoma
Smoking	Lung carcinoma

Host defense

• Tumor Antigens:

- **Tumor-specific antigens: present only on tumor cells.**
- **Tumor-associated antigens: present on tumor cells and some normal cells.**

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

• Tumor antigens may:

- **Result from gene mutations and tumor suppressor genes : 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 : HPV , EBV** which incorporates itself with the host DNA, the resulting proteins will be expressed on the cell membrane
- **Be differentiation specific: PSA [prostate specific antigen] 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:** normal embryonic antigen but absent in adults….in some tumors it will be re-expressed

e.g:

CEA (causes colon carcinoma) ,Alpha fetoprotein (causes liver carcinoma)

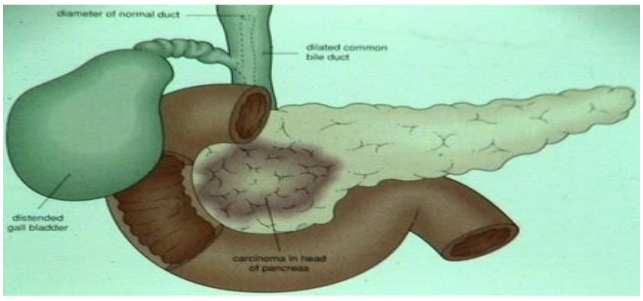
• Antitumor mechanisms involve:

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

Clinical features

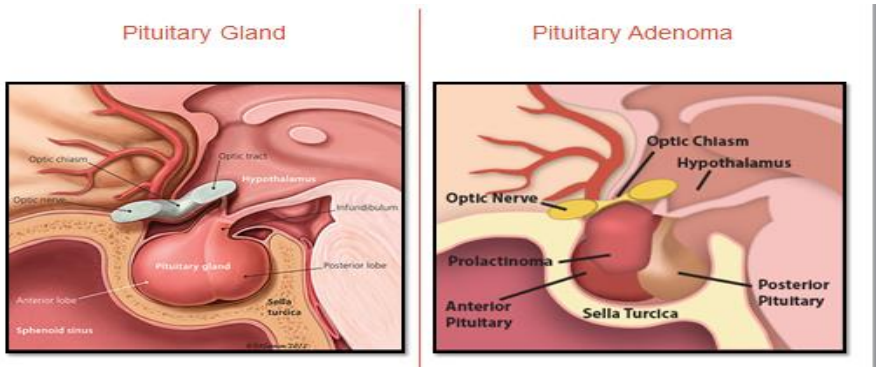
• Tumors cause problems because :

1) **Location and effects on adjacent structures: even small rumors if present in a sensitive area can be dangerous.**



e.g:

- (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**).

2) **Tumors may cause bleeding and secondary infections or fractures:**

- lesion ulcerates adjacent tissue and structures

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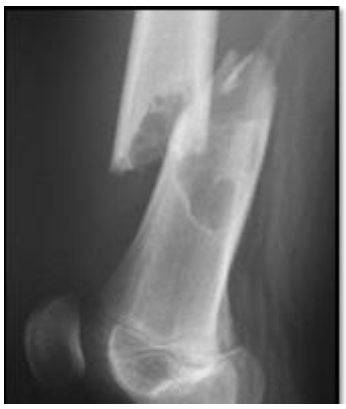
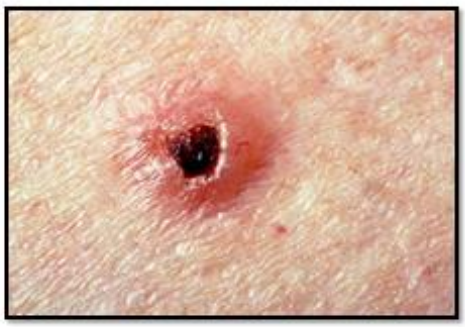
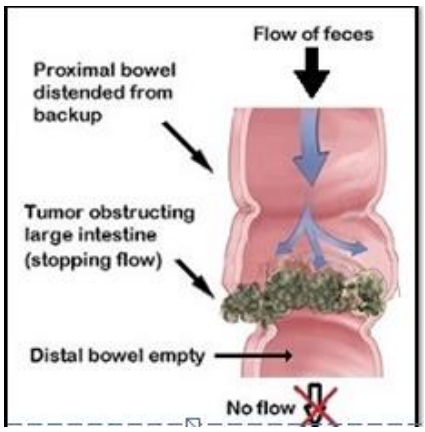
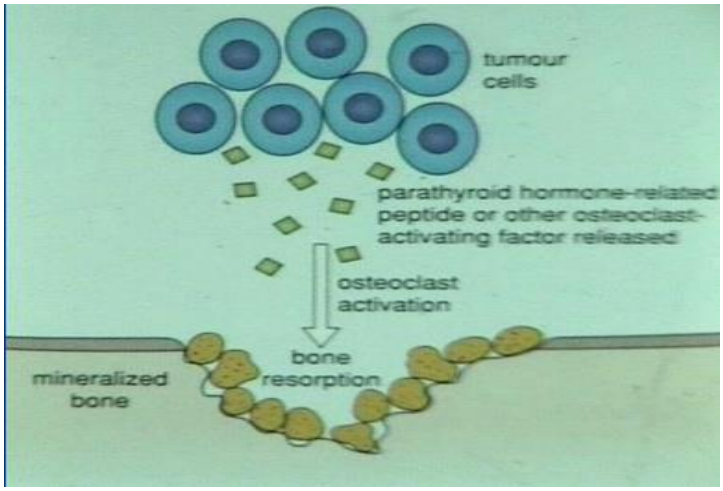




3)Symptoms that result from rupture, obstruction or infraction:



EFFECT OF A TUMOR ON THE HOST



4) Effects on functional activity

- hormone synthesis occurs in neoplasms arising in endocrine glands:
  - **adenomas and carcinomas** of **β cells** of the islets of the **pancreas** produce **<u>hyperinsulinism</u>**.
  - Some adenomas and carcinomas of the adrenal cortex elaborate **<u>corticosteroids.</u>**
    - aldosterone induces sodium retention, hypertension, and hypokalemia
- Usually such activity is associated with benign tumors more than Carcinomas

5)Cancer cachexia:

- **Usually accompanied by weakness, anorexia 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): TNF suppresses appetite.
    - 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.

6) 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.
- They may represent significant clinical problems and may be lethal.
- They may mimic metastatic disease.

- **The most common paraneoplastic syndrome are:**
    - Hypercalcemia
    - Cushing syndrome (causal agents ACTH)
    - Nonbacterial thrombotic endocarditis
    - The most often neoplasms associated with these syndromes:
        - **Lung and breast cancers** and **hematologic malignancies**

P araneoplastic 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	-5hydroxy -indoleacetic acid) 5 - HIAA (	Metastatic malignant carcinoid tumors

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

Grading :

The grading of a cancer attempts to establish some estimate of its aggressiveness (عدوانية أو خطورة) or level of malignancy based on the **cytologic** differentiation of tumor cells and the number of mitoses within the tumor.

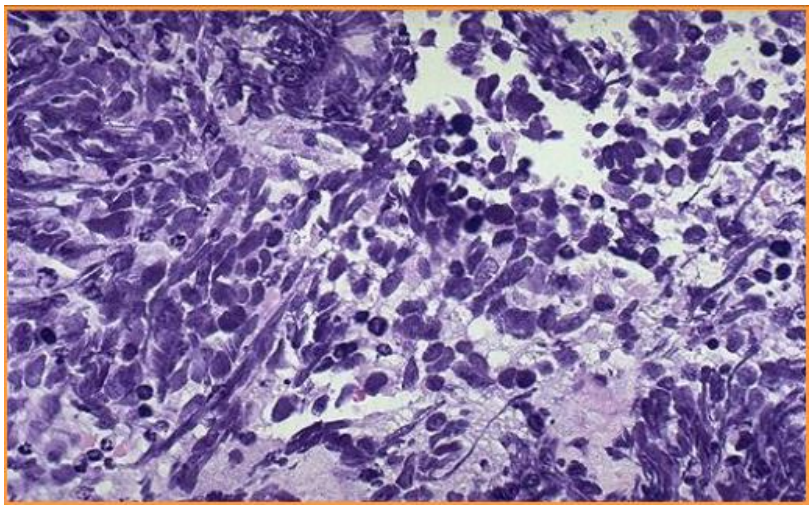
Grade I: Well differentiated

Grade II: moderately differentiated

Grade II: poorly differentiated

Grade IV: anaplastic (undifferentiated)

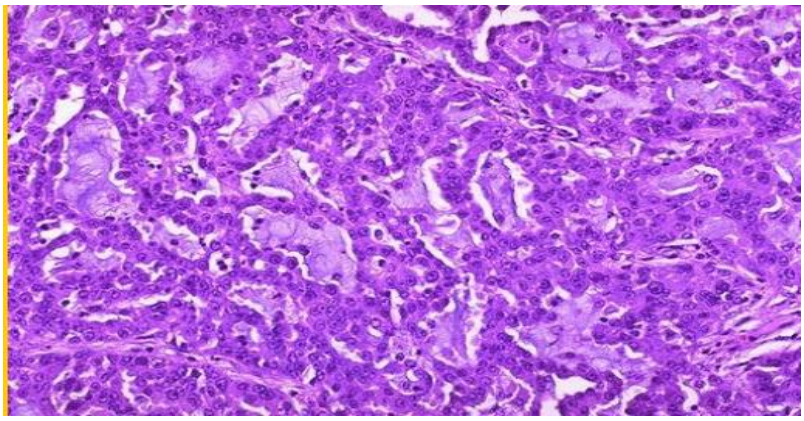
* usually, the more the grade the more aggressive it is.



Oat cell carcinoma of the lung
-Undifferentiated carcinoma
-Grade IV

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.



Adenocarcinoma of the colon
-Well differentiated carcinoma

A well differentiated neoplasm is composed of cells that closely resemble the cell of origin.

Staging:

Staging of cancers is based on :

- the size of the primary lesion
- its extent of spread to regional lymph nodes
- the presence or absence of metastases. (the extent of the spread of neoplastic in the body)

-Size
-Regional lymph nodes involvement
-Presence or absence of distant metastasis

TNM system

Clinical Staging

-T (primary tumor): T1, T2, T3, T4

-N (regional lymph nodes): N0, N1, N2, N3

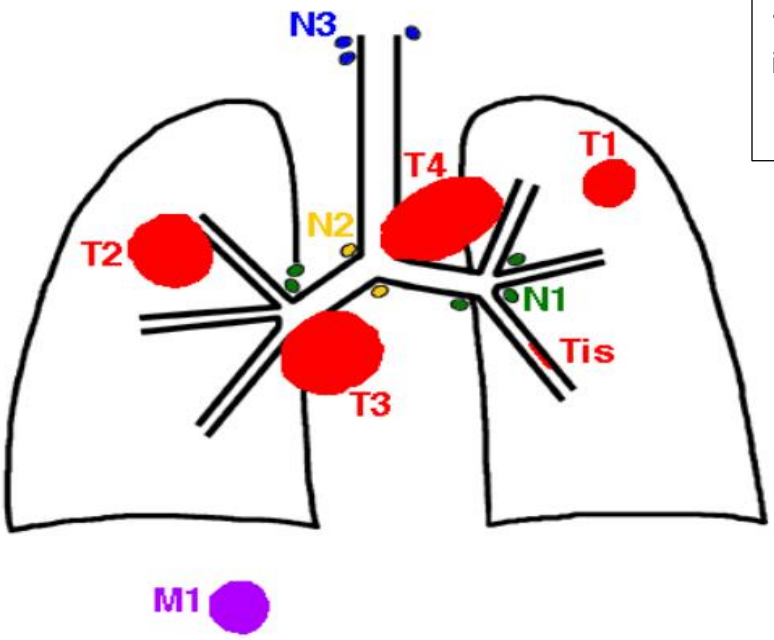
-M (metastasis): M0, M1

-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 :- is there a metastasis or not

TNM staging system in cancer



(NOTE: this table is only for understanding)

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:

Include Microscopic Tissue Diagnosis or cellular diagnosis

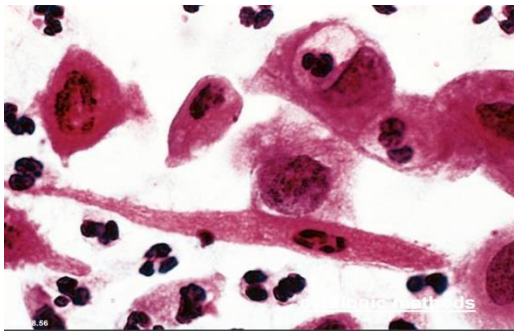
1. The gold standard of cancer diagnosis.
2. Several sampling approaches are available:
   - Excision (removal of whole organ)
   - Biopsy (removal of tissue (Histopathology)) .
   - fine-needle aspiration (removal of individual cells – cytopathology) .
   - Frozen section. (quick diagnosing)
   - Cytologic (papanicolaou) smears: neoplastic cells are less cohesive than others and therefore shed into fluids or secretions.
   - Flow cytometry : used routinely in the classification of leukemia and lymphoma.
   - Immunohistochemical stains.

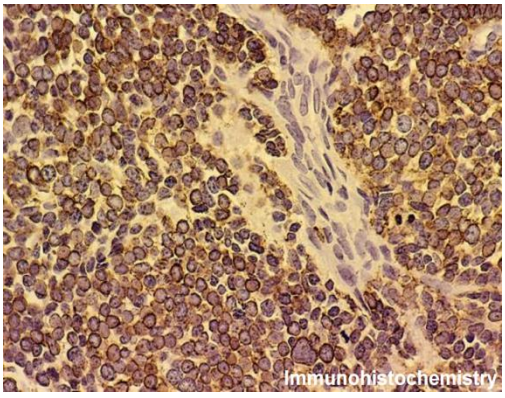
Immunohistochemistry (antigen antibody reactions)

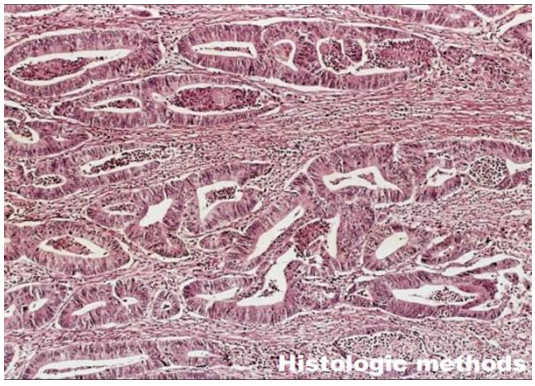
if the tissue is extremely undifferentiated then we put antibodies and look for positive reactions with the antigens , these antigenic expressions specify exactly which cancer cell it is.

-offers a powerful adjunct to routine histologic examination.

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







B. Biochemical assays:

- Useful for measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum. مثال لو شخص سوينا له عملية ازالة ورم يختفي الأنتيجين حق الورم بعدين اسوي له تحاليل كل فترة عشان اشوف الجين رجع او لا

- Useful in screening, determining the effectiveness of therapy and detecting tumor recurrences.
- Elevated levels may not be diagnostic of cancer (PSA). (prostatic specific antigen)
- Only few tumor markers are proved to be clinically useful, example CEA (colon cancer) and α-fetoprotein (hepatocellular carcinoma) .

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. (t(9,22))
- **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)

- **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.

Best Wishes and Good Luck

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