# Neoplasia 2020/21 lecture 9

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# ILOS

- 1.list the main environmental causative agents of cancer.
- 2. understand the difference between direct and indirect acting chemical carcinogens.
- 3. understand the pathogenesis of cancer development due to several etiologic agents.

# Carcinogenesis.. review

- Carcinogenesis, as we discussed in the previous lectures, results from one single clone that acquires certain mutations which allow this clone to proliferate rapidly.
- As the tumor mass grows, extra mutations occur that add certain phenotypes to this mass ( subclones are formed).
- 8 phenotypic hallmarks are needed to sustain the tumor mass.
- These hallmarks are acquired via mutations.
- No single mutation is enough for transformation of cells.
- Several mutations are needed to acquire the 8 hallmarks.
- One mutation might result in several hallmarks.

- SO: how do these mutations are acquired… what are the etiologic agents that can cause cancer???
- This is the main topic of this lecture.

# Etiology of cancer

-Cancer can be caused by inherited or acquired mutations.

-We discussed many of the inherited mutations in the previous lectures: like RB, BRACA …

-Environmental factors that cause mutations are mainly:

- Chemicals
- Radiation
- infections

# Chemical carcinogenesis

- One of the first cancers linked to chemical carcinogens is scrotal squamous cell carcinoma
- Sir Percival Pott .. A London surgeon noted that scrotal cancer is common in chimney sweeps and he thought it is related to soot exposure.
- Danish chimney sweeps guild ruled that its members bathe daily
- This reduced scrotal cancer.. It is a very successful story about how to prevent cancer with life style changes ( a daily bath in this instance!)

So: chemicals can cause cancer

# Chemical carcinogens

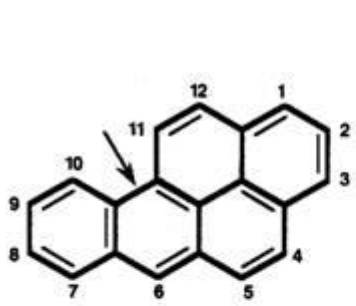
- Chemicals cause cancer directly ( direct acting agents) or by being converted to a carcinogenic metabolite ( indirect acting agents)

# Direct acting agents

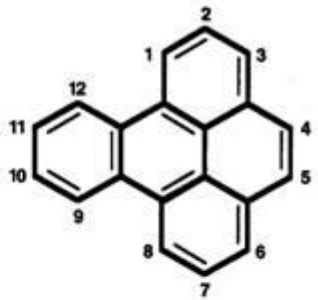
- These are weak carcinogens that don’t need metabolic conversion
- Examples: chemotherapy drugs (alkylating agents) can cause cancer, usually leukemia

# Indirect acting agents

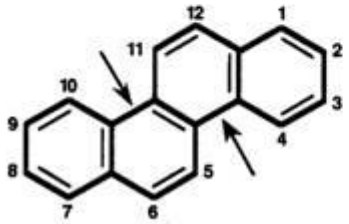
- These need metabolic conversion to become carcinogenic
- Example: polycyclic hydrocarbons which are present in fossil fuel



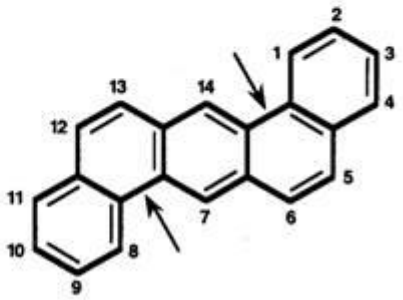
Benzo[*a*]pyrene



Benzo[*e*]pyrene



Chrysene



Dibenz[*a*,*h*]anthracene

# Indirect acting agents

- Benzo (a) pyrene is a polycyclic hydrocarbon present in cigarette smoke and can cause lung cancer
- polycyclic hydrocarbons are also present in smoked meat .Produced from animal fat during broiling meat.
- The main active product in polycyclic hydrocarbons is epoxides
- Epoxides react with DNA, RNA and cellular proteins

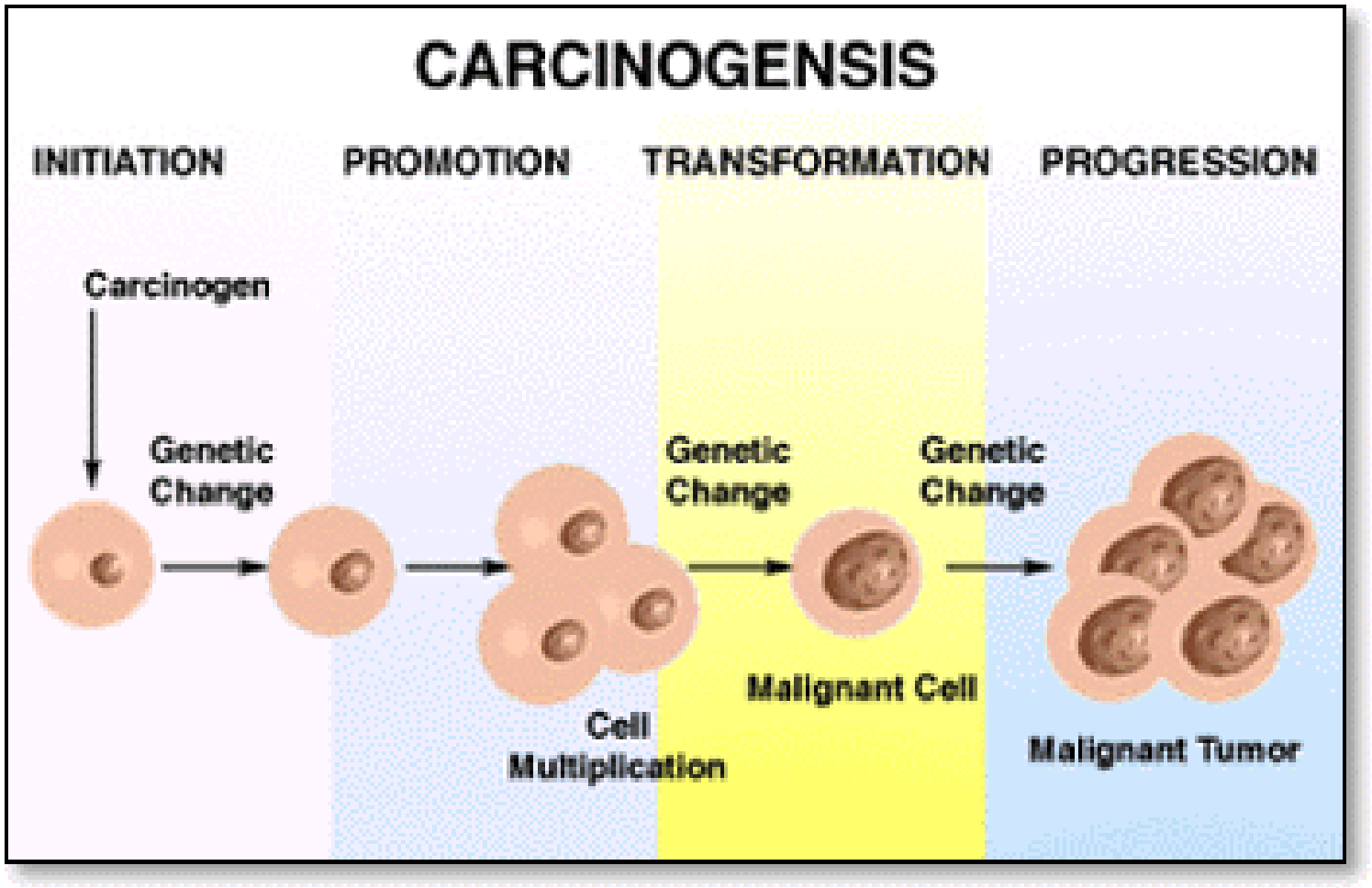
# Indirect agents

- Aromatic amines and azo dyes. Example beta naphthalamine… increases bladder cancer in workers in the aniline dye and rubber industries.
- Aflatoxin B .. Is a naturally occurring agent produced by aspergillus which is a fungus that grows on improperly stored grains and nuts. It increases incidence of hepatocellular carcinoma
- Nitrites used as food preservatives can produce nitrosamines which are probably carcinogenic.. Linked to gastric cancer

# Mechanisms of action of chemical agents

- Chemical carcinogens have reactive electrophile group that form chemical adducts with DNA, RNA and proteins
- Any gene can be a target for chemicals.. But mostly mutated are RAS and TP53.
- Aflatoxin causes TP53 mutation

- Some chemical carcinogens are augmented by subsequent promoters (hormones, drugs, phenols)
- The promoters are not carcinogenic by themselves .
- Promoter effect has to come after the initiator (tumorigenic substance)
- How do promoters work???? They induce cell proliferation which causes clonal expansion of the mutated cells.. These mutated cells now proliferate and accumulate additional mutations


CARCINOGENSIS
INITIATION
PROMOTION
TRANSFORMATION
PROGRESSION
Carcinogen
Genetic Change
Genetic Change
Genetic Change
Cell Multiplication
Malignant Cell
Malignant Tumor

# Radiation carcinogenesis

- Miners of radioactive elements have 10 fold increase of lung cancer
- Survivors of atomic bombs in Hiroshima and Nagasaki .. Have increased incidence of leukemia… latent periods of 7 years. They also have increased risk of thyroid, breast ,colon and lung cancer
- Chernobyl nuclear power accident.. Also increased cancer
- Therapeutic radiotherapy of head and neck can cause papillary thyroid cancer years later

- Ionizing radiation causes chromosomal breakage, translocation and less commonly point mutations
- Ultraviolet radiation causes pyrimidine dimers.. Not repaired in xeroderma pigmentosum causing increased risk of skin cancers
- Non-melanoma skin cancers (squamous cell carcinoma and basal cell carcinoma) are associated with total accumulation of UV exposure
- Melanoma associated with intense intermittent exposure.. Like in sunbathing

# Viral and microbial carcinogens

- Oncogenic RNA viruses: HTLV 1
- Oncogenic DNA viruses: human papillomavirus , EBV, hepatitis B and C viruses
- Bacteria: H pylori

# HTLV 1= human T lymphocyte virus 1

- A retrovirus involved in T cell lymphoma/ leukemia
- The virus is endemic in Japan and the Caribbean
- It targets CD 4 T cells
- Transmitted sexually and through blood or breast feeding
- Leukemia develops in 3- 5% of those infected after 20-50 years
- Very latent period.. Suggests multistep process of accumulation of multiple oncogenic mutations
- The virus does not encode an oncogene and is not integrated to a cellular oncogene

# HPV = human papilloma virus

- There are several types of HPV. Some produce benign warts (benign squamous cell papillomas), others cause cancer
- HPV 16 and 18 cause cancer . 16 and 18 are called high risk HPV

- Cancers associated with HPV:

1. Squamous cell carcinoma of the cervix and anogenital region
2. Oropharyngeal carcinoma, especially those arising in the tonsils

# HPV

- Carcinogenic effect of HPV is related to two viral genes E7 and E6
- E7 binds RB protein and releases E2F
- E7 also inactivates CDKIs
- E6 binds to and degrades p53

- There are several HPV subtypes, some are high risk and others are low risk.
- High risk HPV are the ones linked to cancer.

# Differences between high and low risk HPV types

- E6 of high risk HPV has higher affinity to p53 than low risk HPV. And E7 of high risk HPV has higher affinity to RB
- Low risk viral genes remain in nonintegrated episomes whereas high risk ones are integrated in cell genome causing overexpression of E6 AND E7
- Cells with integrated viral genome show genetic instability.

# High risk HPV

- Cells infected with high risk HPV have decreased RB and p53 effect
- So: there is loss of tumor suppressor genes, inhibited apoptosis, no senescence, impaired DNA repair
- However, in experimental models HPV alone is not enough for transformation… a mutated oncogene is needed

- Importance of HPV in cervical cancer supported by protection of this cancer by anti HPV vaccine

# EBV = Epstein Barr virus

- It Causes:

1. Burkitt lymphoma
2. B cell lymphomas especially in people with low immunity and HIV infection
3. Hodgkin lymphoma
4. Nasopharyngeal carcinoma
5. T cell lymphomas
6. Gastric carcinoma
7. Natural killer lymphoma
8. Sarcomas especially in the immunocompromized

# EBV

- EBV infects B lymphocytes by attaching to CD21 receptor
- This leads to polyclonal B cell proliferation
- One of the EBV genes = LMP1(latent membrane protein 1) act as an oncogene
- LMP 1 promotes B cell proliferation through NF- kB and JAK/STAT pathways
- LMP 1 also activates BCL2.. So prevents apoptosis
- LMP also induces angiogenesis

- EBNA2 is another EBV gene that activates cyclin D and other cellular oncogenes
- Viral cytokines vIL 10 prevents macrophages from activating T cells and killing virally infected cells

- Immunocompetent person.. Polyclonal expansion of B cells is controlled and the patient is either asymptomatic or has infectious mononucleosis
- To become mutagenic, EBV needs the infected cells to evade the immune system
- In endemic areas other coinfections like malaria impair the immune system
- LMP1 is recognized by the immune system,, not expressed in Burkitt
- Myc mutations substitute for LMP
- All Burkett has MYC mutation

- People with T cell suppressed immunity … LMP is expressed
- Nasopharyngeal carcinoma..LMP is expressed
- LMP induces angiogenic factors like VEGF, FGF, MMP9 AND COX 2

# Hepatitis B and C viruses

- 70-85% of hepatocellular carcinomas are associated with B or C
- Hep B and C do not encode an oncogene
- Hep B genome is integrated in hepatocyte genome but with no consistent pattern

- So how they cause cancer.. It’s thought that the effect is multifactorial and related to immunologically mediated chronic inflammation with regeneration and genomic instability

- Chronic inflammation and immunologic reaction is associated with increased cytokines, growth factors, angiogenic factors
- Also ROS produced and can cause DNA damage

- So: this is an example of inflammation as an enabler of malignancy

- NF-KB pathway is important here.. It blocks apoptosis

# Other mechanisms

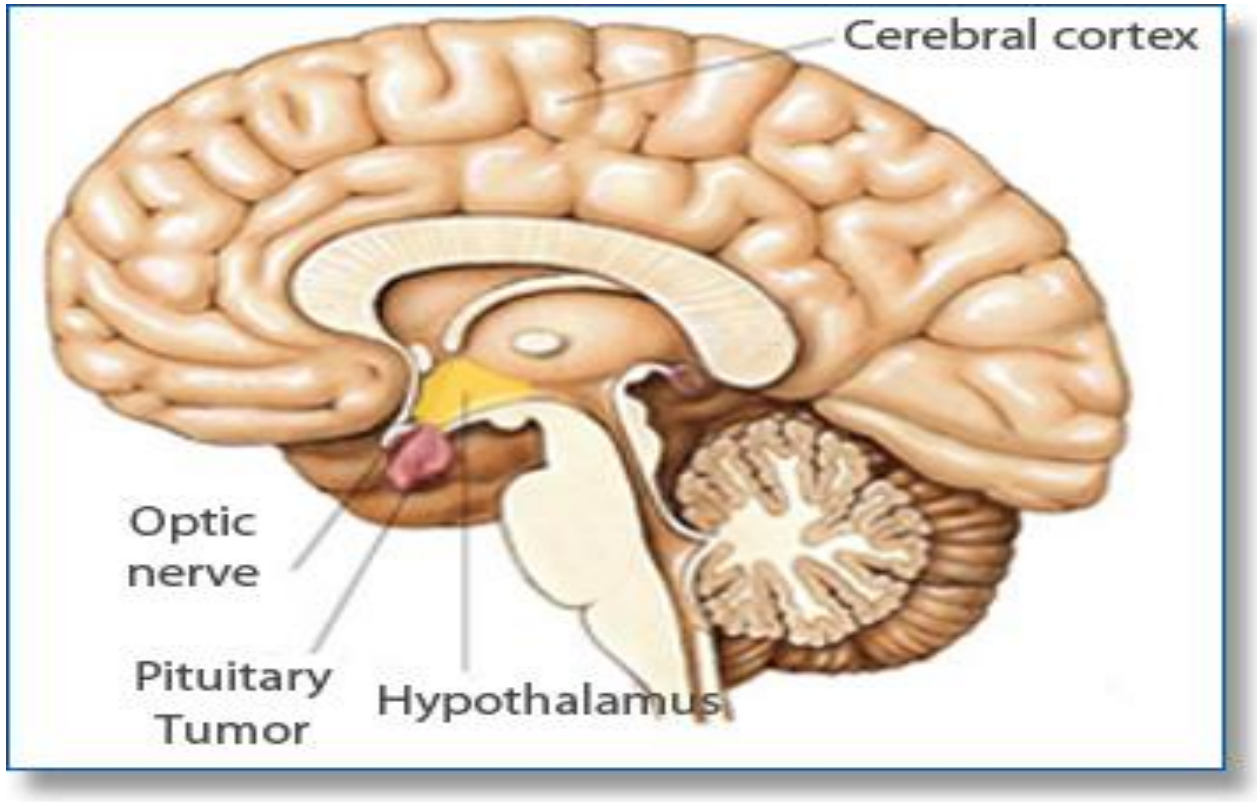
- HBx gene in hep B can activate oncogenes
- Viral genome integration probably plays a role in causing chromosomal rearrangements
- Hep C core protein can also stimulate oncogenes

# Clinical aspects of malignancy

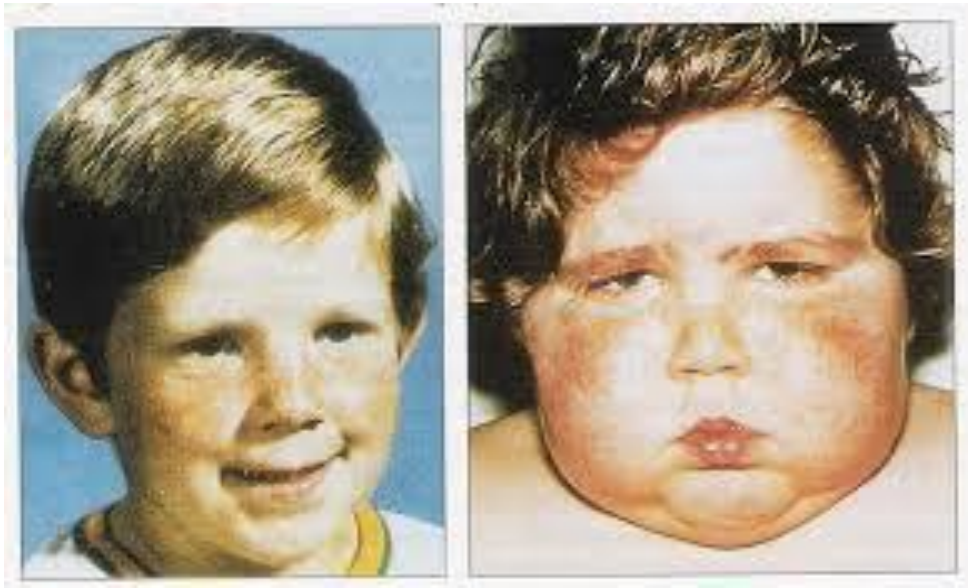
# Tumor location

- Even small tumors can be dangerous
- CNS tumors can cause increased intracranial pressure

# Effects of tumors on the host/ location effect

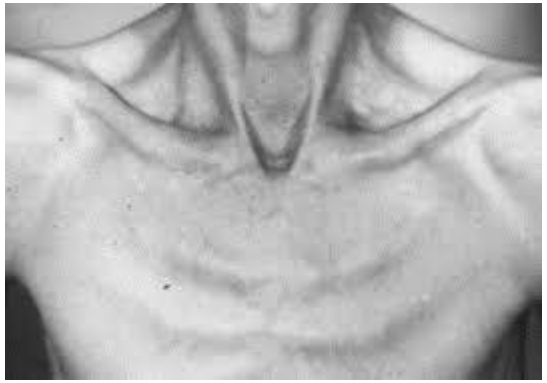


# Effects by hormonal secretions
# example pituitary adenoma can secrete ACTH and cause Cushing syndrome



# Cancer cachexia

- = progressive loss of body fat with associated weakness, anorexia and anemia
- Cachexia is **not** caused by the nutritional demands of the tumor
- There is some correlation between cachexia and the size and extent of spread of the cancer.



# Causes of cachexia

- Anorexia plays a role, however **chemical factors are the main reason**
- **Cachectic patents have high metabolic rate, muscle wasting**
- **TNF produced from macrophages is probably the main factor for these changes**
- Effects of TNF:
- 1. suppresses appetite
- 2.inhibits lipoprotein lipase

ALSO: proteolysis inducing factor that breaks skeletal muscle by ubiquitin proteasome pathway is increased in cancer patients… it causes muscle wasting

- The only satisfactory treatment of cancer cachexia is removal of the primary tumor

# Para-neoplastic syndromes

- = symptoms that cannot be explained by local or distant metastases or by hormones endogenous to the site of origin.
- These are usually caused by ectopic hormone secretion
- Most common para neoplastic syndromes: hyercalcemia, Cushing syndrome, and nonbacterial thrombotic endocarditis
- Most common tumors that are associated with paraneoplastic syndromes: lung, breast and hematologic malignancies

# Helicobacter pylori

- Can cause gastric carcinoma and lymphoma (MALTOMA)
- **H pylori cause cancer by inducing chronic inflammation**
- Sequence: inflammation, atrophy, metaplasia, dysplasia, Cancer
- This sequence needs decades to be completed and it occurs only in 3% of people with H pylori infection
- H pylori also have genes that are tumorigenic like cagA= cytotoxic associated A which simulates growth factors

# Hyercalcemia as paraneoplastic

- Caused by
- 1. PTHrP (  parathyroid hormone related protein)
- 2.TGF alpha activate osteoclasts and the active form of vit D
- 3.TNF and IL1

- **NOTE: Skeletal mets cause hyperkalemia but this is not a paraneoplastic syndrome**

# How H pylori cause lymphoma

- H pylori infection causes  T cell activation that result in B cell proliferation which starts as polyclonal proliferation
- Accumulation of mutation causes monoclonal expansion
- Host genetic factors like polymorphisms in  TNF and IL1 polymorphisms  play a role in the susceptibility to develop MALTOMA
- Early in the disease eradication of  H pylori cures the lymphoma by removing antigenic cause of T cell proliferation

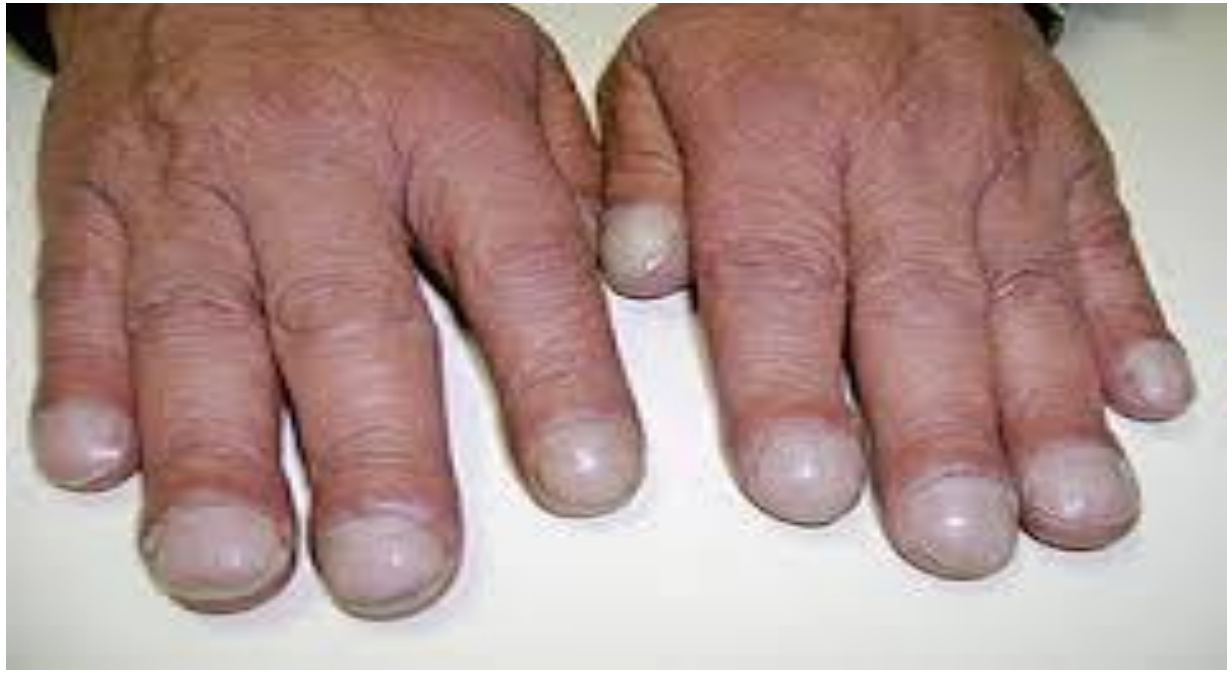
# Paraneoplastic syndromes

Table 6.6 Paraneoplastic Syndromes

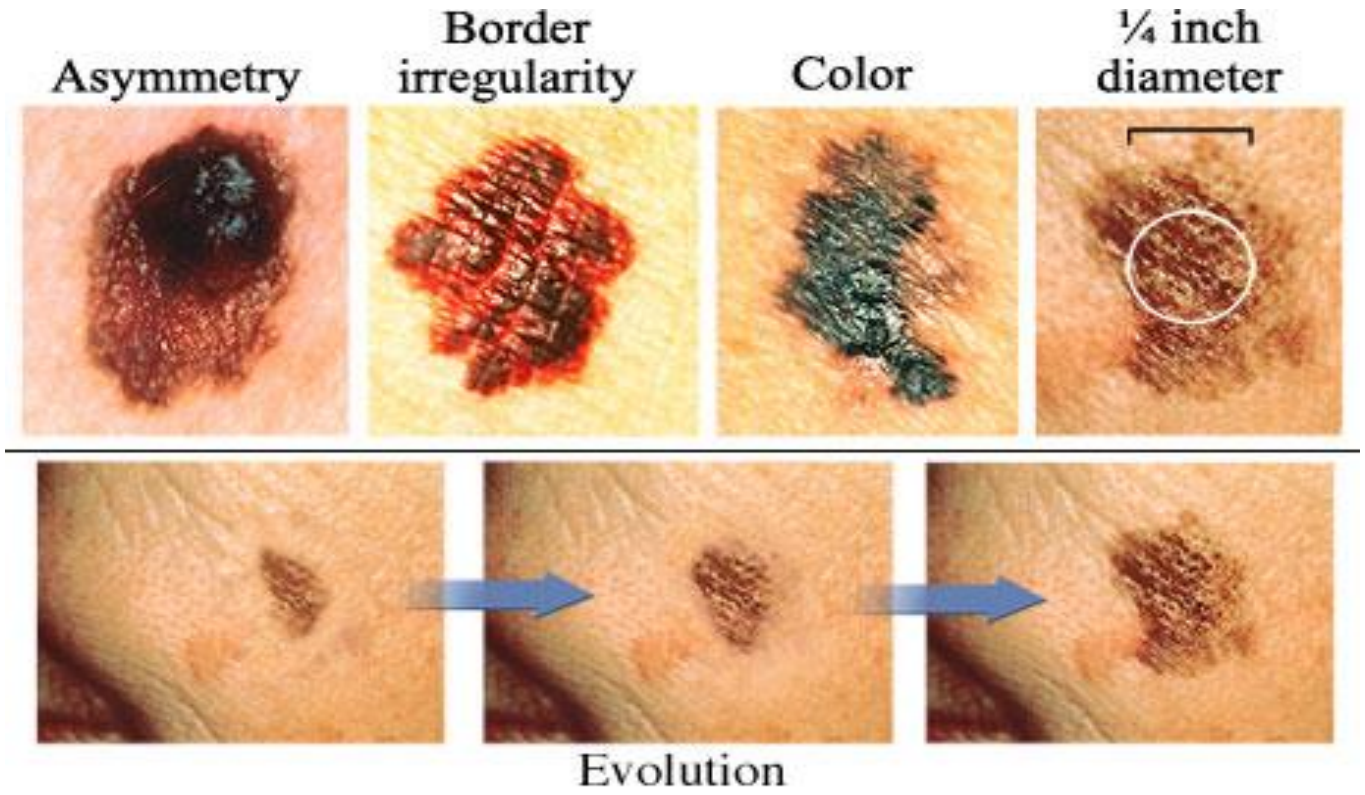
| Clinical Syndrome | Major Forms of Neoplasia | Causal Mechanism(s)/Agent(s) |
|---|---|---|
| **Endocrinopathies** | | |
| Cushing syndrome | Small cell carcinoma of lung<br>Pancreatic carcinoma<br>Neural tumors | ACTH or ACTH-like substance |
| Syndrome of inappropriate anti-diuretic hormone secretion | Small cell carcinoma of lung; intracranial neoplasms | Anti-diuretic hormone or atrial natriuretic hormones |
| Hypercalcemia | Squamous cell carcinoma of lung<br>Breast carcinoma<br>Renal carcinoma<br>Adult T cell leukemia/lymphoma | Parathyroid hormone–related protein, TGF-α |
| Hypoglycemia | Fibrosarcoma<br>Other mesenchymal sarcomas<br>Ovarian carcinoma | Insulin or insulin-like substance |
| Polycythemia | Renal carcinoma<br>Cerebellar hemangioma<br>Hepatocellular carcinoma | Erythropoietin |
| **Nerve and Muscle Syndrome** | | |
| Myasthenia | Bronchogenic carcinoma, thymoma | Immunologic |
| Disorders of the central and peripheral nervous systems | Breast carcinoma, teratoma | Immunologic |
| **Dermatologic Disorders** | | |
| Acanthosis nigricans | Gastric carcinoma<br>Lung carcinoma<br>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<br>Bronchogenic carcinoma<br>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 |

*ACTH*, Adrenocorticotropic hormone; *IL-1*, interleukin-1; *TGF-α*, transforming growth factor-α; *TNF*, tumor necrosis factor.

# Clubbing of fingers is paraneoplastic, mainly due to lung cancer… etiology is unknown



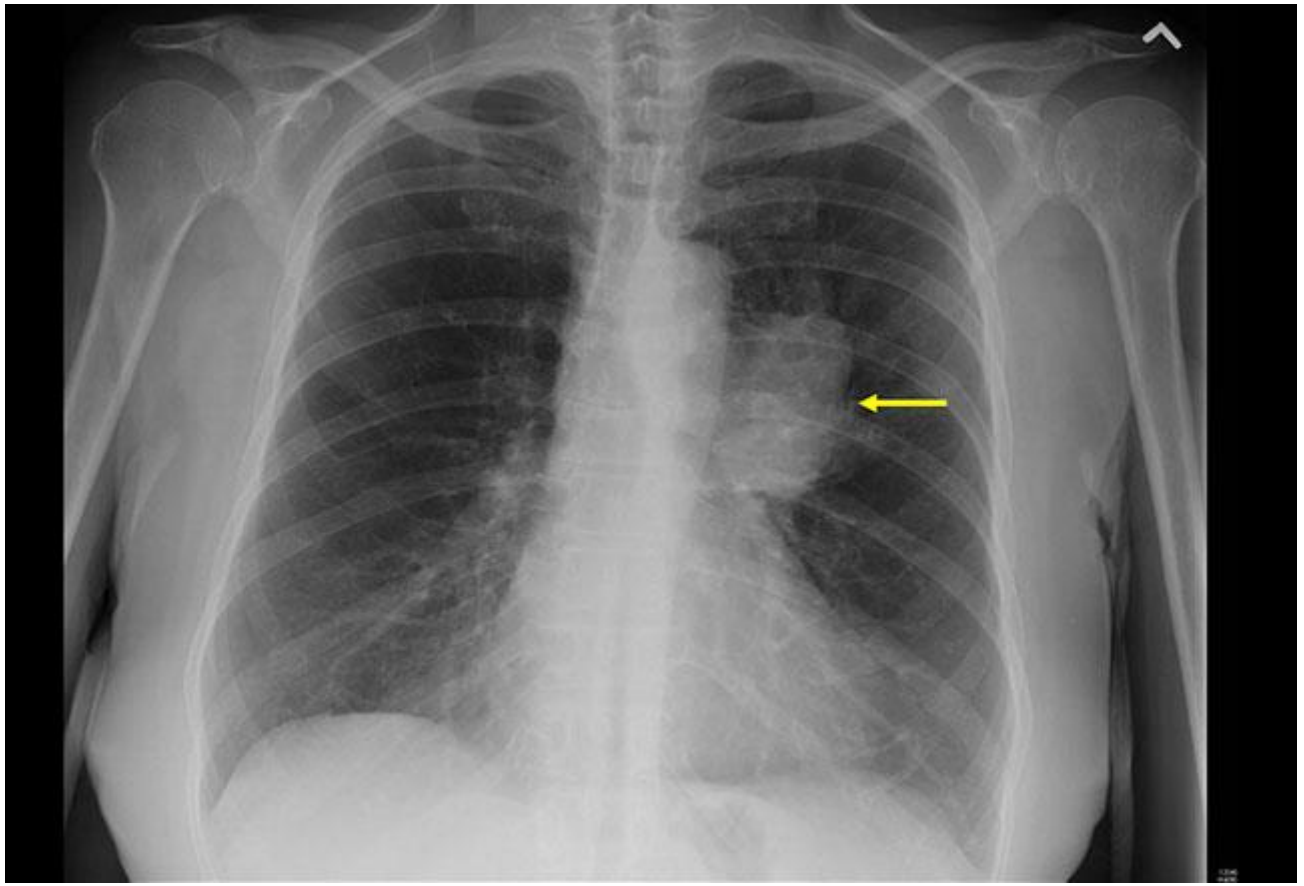
# Clinical


Asymmetry
Border irregularity
Color
¼ inch diameter
Evolution

# Lab diagnosis of cancer

- To diagnose cancer you need correlation between : clinical , radiologic and lab methods
- **Clinical**: cancer presents as hard, fixed infiltrative tumors
- **Radiology**: X ray, CT , MRI , PET scans
- **Lab**: morphologic methods, tumor markers, and molecular diagnosis

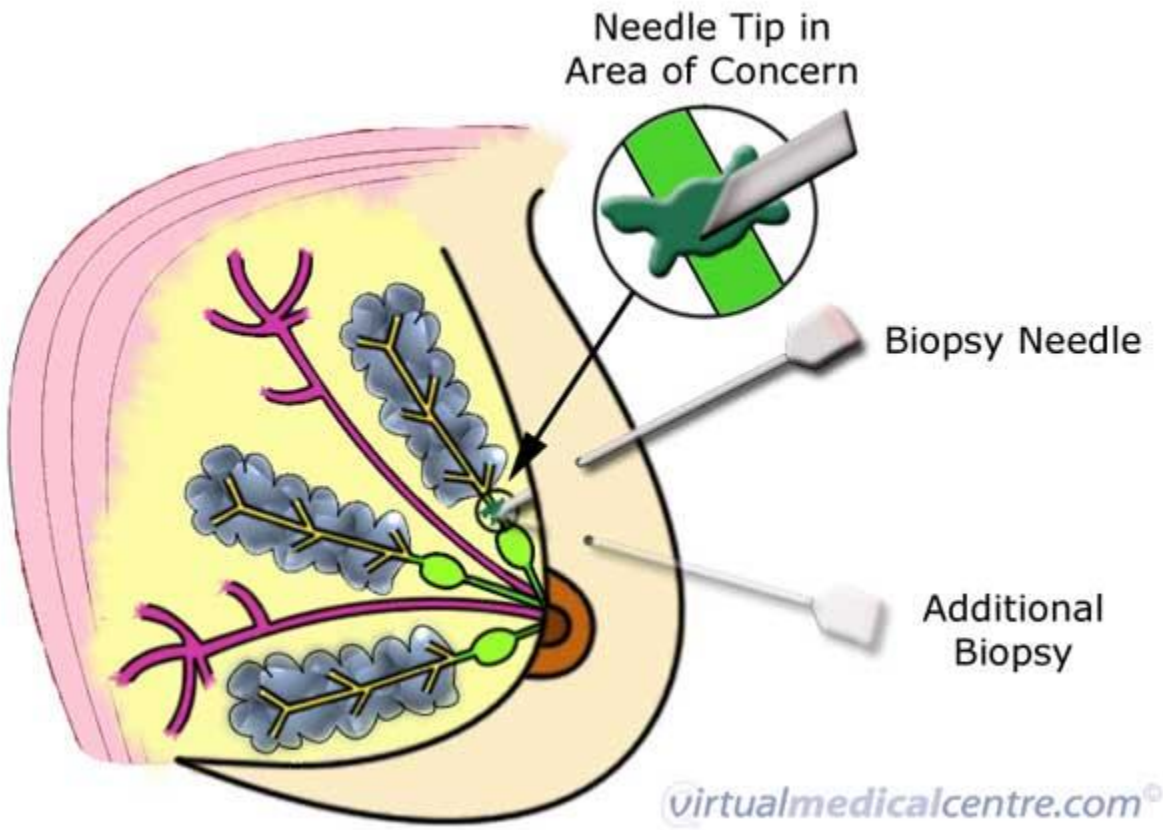
# Imaging



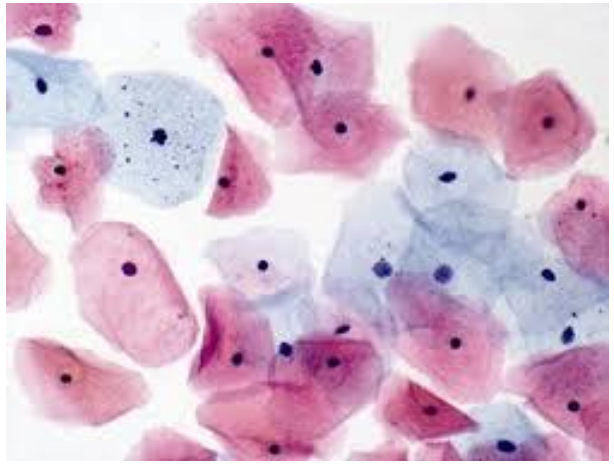
# Lab tests/ morphology

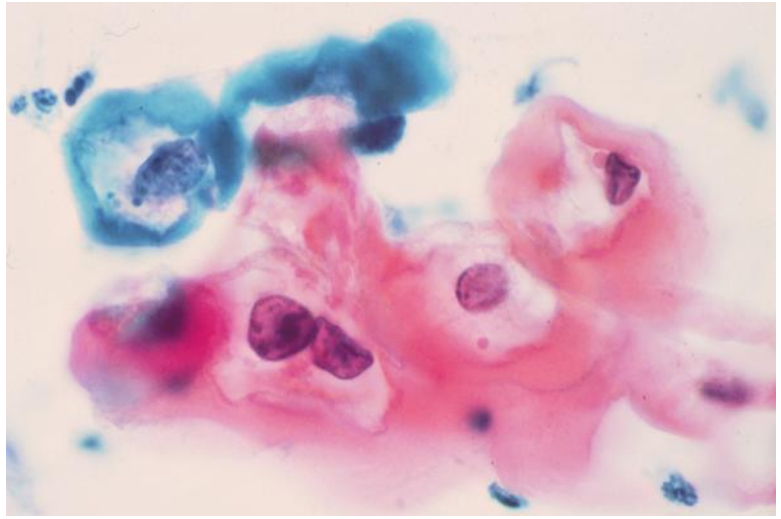
- **Cytologic smear**: cervical smear, sputum..
- FNA= **fine needle aspiration**, if a mass is easily accessible like: breast, thyroid. Or accessible by imaging technique: under imaging guidance FNA can be taken
- **Incisional biopsy**: representative sample taken
- **Excisional biopsy**: all the mass removed, usually with safety margin
- **Frozen section**: for quick diagnosis while patient still on the surgical table

# FNA.. Breast cancer

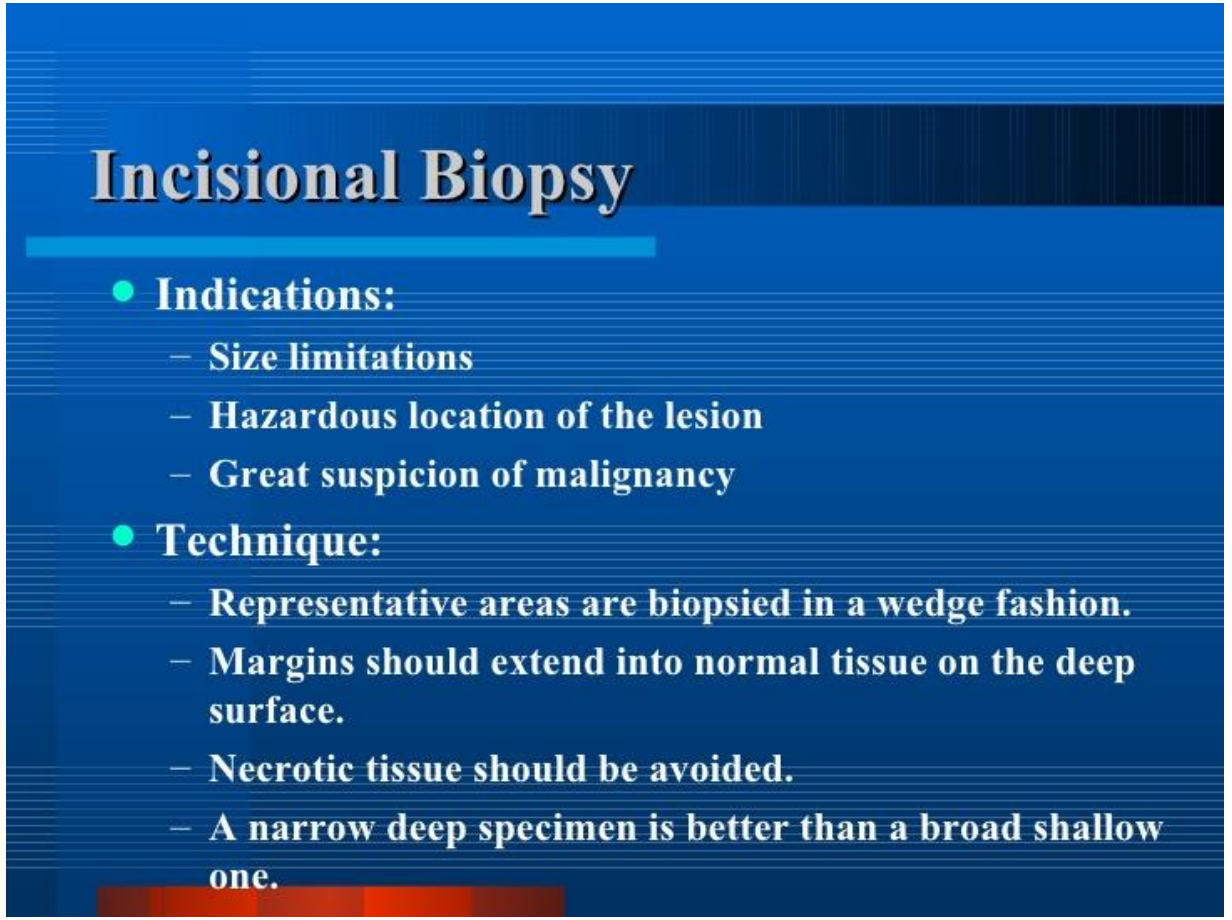


# Cytologic smear
# = pap smear





# Incisional biopsy

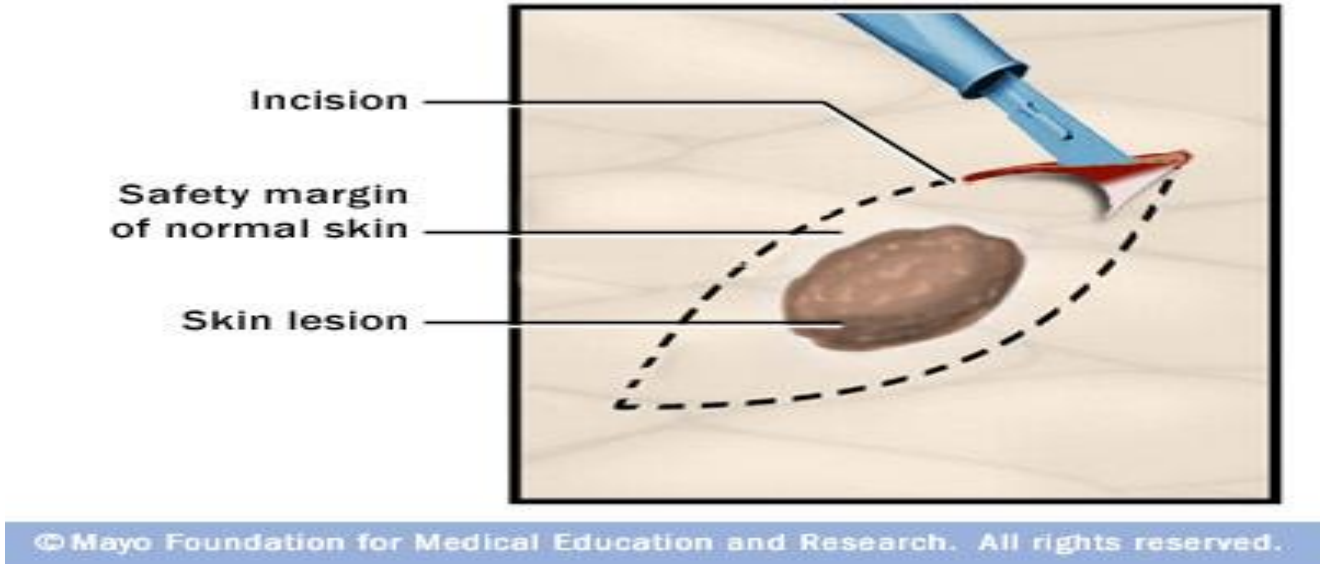


# Excisional Biopsy

An excisional biposy implies the complete removal of the lesion.

- Indications:
  - Should be employed with small lesions. Less than 1cm
  - The lesion on clinical exam appears benign.
  - When complete excision with a margin of normal tissue is possible without mutilation.

# When you excise, excise with a safety margin



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# Tumor markers

- Tumor markers: enzymes, hormones ..
- Cannot be used for definitive diagnosis of cancer
- But can be used for screening or to follow up response to therapy  or detect recurrence

# PSA as a tumor marker

- PSA( prostate specific antigen) can be elevated in hyperplasia .. No level ensures that the is no cancer .. It has low sensitivity and low specificity
- PSA good for residual disease or recurrence

# Tumor markers

- CEA (carcinoembryonic antigen) raised in  colon, pancreas stomach, and breast cancer.
- Alpha feto protein .. Hepatocellular carcinoma and yolk sac tumors
- CEA and alpha feto also increased in nonneoplastic conditions
- With treatment these markers  disappear… if they reappear this means recurrence.

# Frozen section

# Frozen section

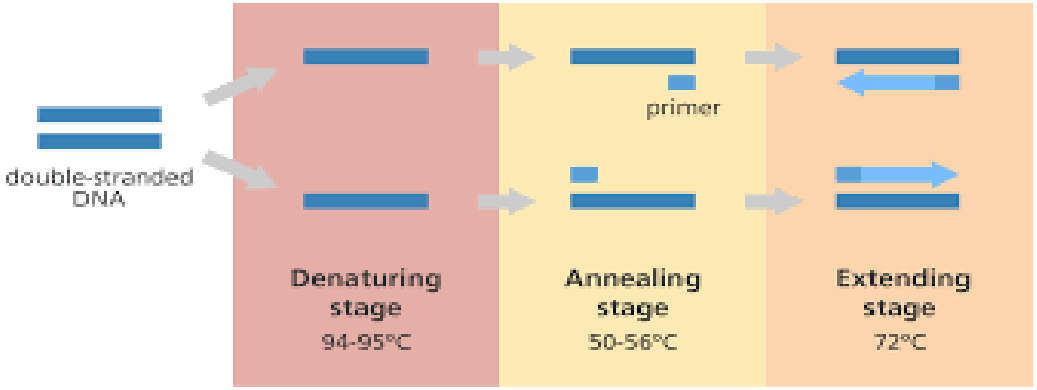
- Used to decide management during the surgery

# Molecular diagnosis

- PCR: polymerase chain reaction can tell if a lymphoid growth is monoclonal ( neoplastic) or polyclonal ( reactive.
- It detects the special rearrangements of gene receptor antigens in B and T cells

- Also PCR and FISH can detect the presence of translocations… important for tumor diagnosis.

- Polymerase chain reaction (**PCR**) is a technique used in molecular biology to amplify a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.



- Thanks and Good luck