Neoplasia 2022/23 lectures 9 and 10

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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

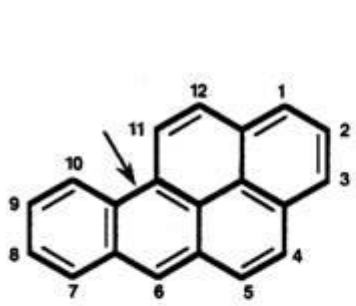
- Chemicals cause cancer directly (direct acting agents) or by being converted to a carcinogenic metabolite (indirect acting agents)

Direct acting agents

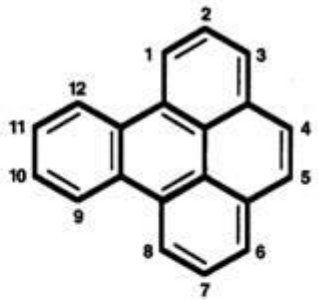
- These are weak carcinogens that don’t need metabolic conversion
- Examples: chemotherapy drugs (alkylating agents) can cause cancer, usually leukemia

Indirect acting agents

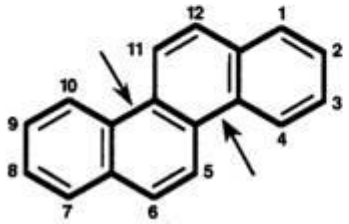
- These need metabolic conversion to become carcinogenic
- Example: polycyclic hydrocarbons which are present in fossil fuel



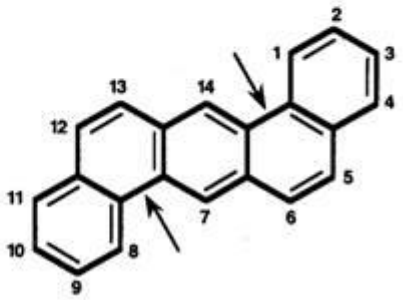
Benzo[*a*]pyrene



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

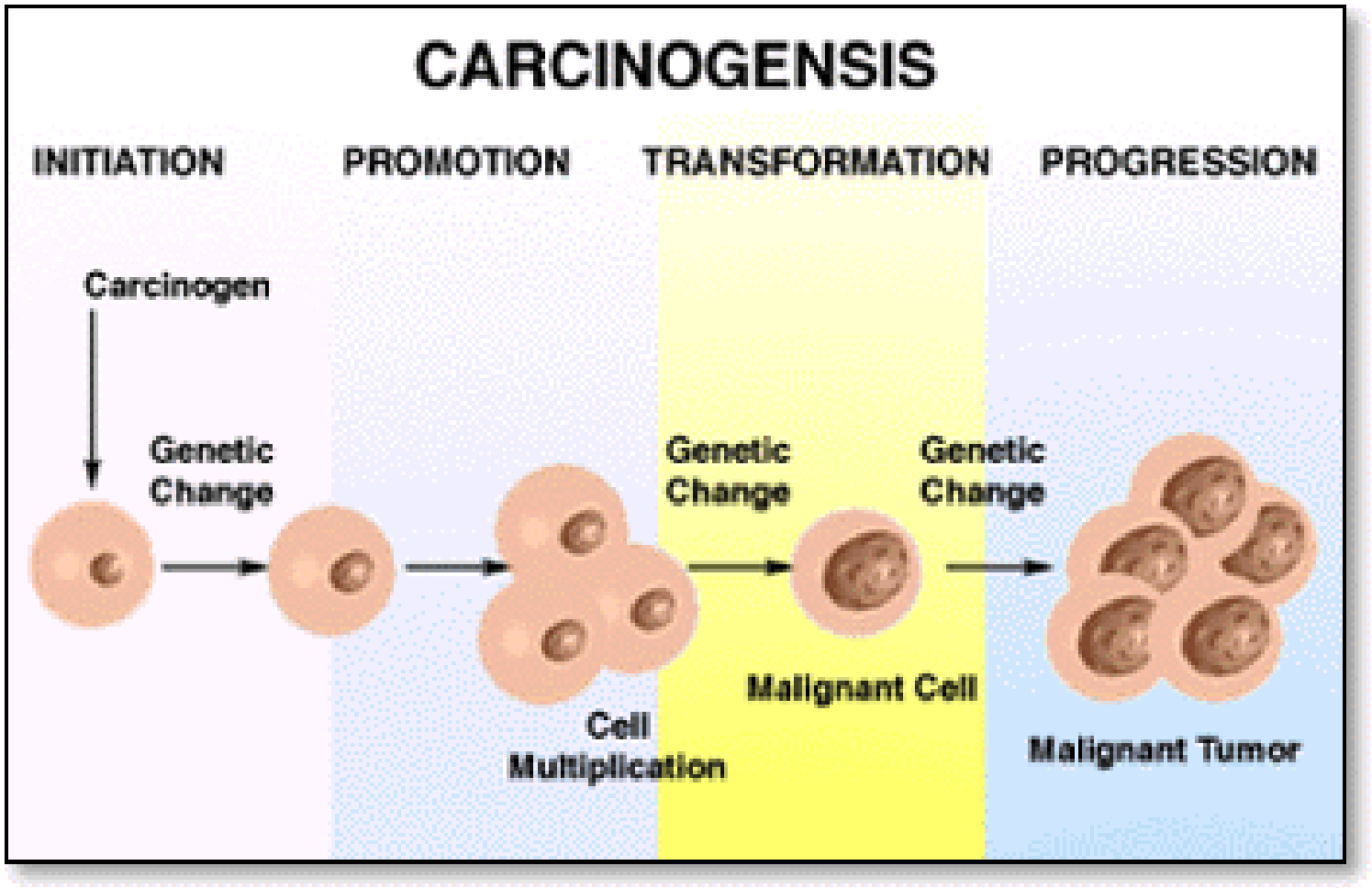
Indirect agents

- 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, hepatitis C
- Oncogenic DNA viruses: human papillomavirus , EBV, hepatitis B
- 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

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 and nasopharyngeal carcinoma

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

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

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 (reactive oxygen species) produced and can cause DNA damage

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

Helicobacter pylori

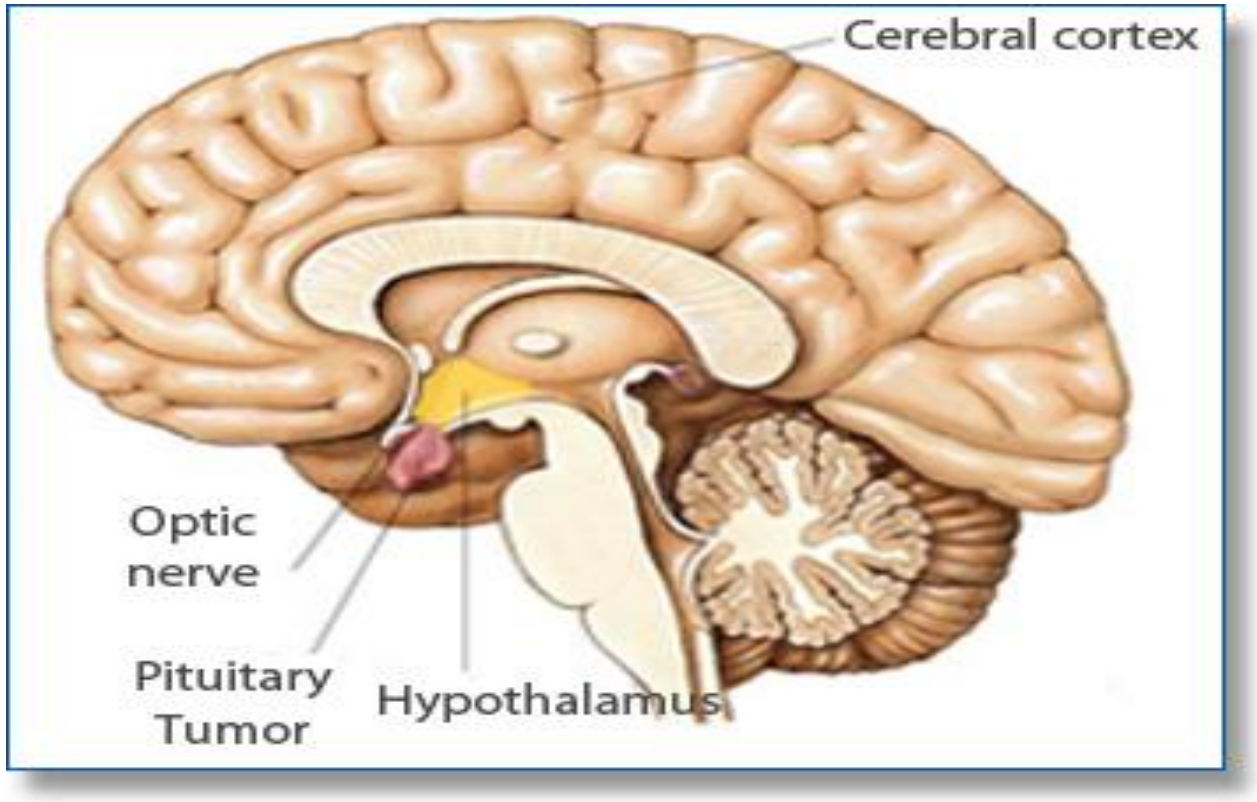
- Can cause gastric carcinoma and lymphoma (MALTOMA)
- **H pylori cause cancer by inducing chronic inflammation**
- Sequence: inflammation, atrophy, metaplasia, dysplasia, Cancer
- This sequence needs decades to be completed and it occurs only in 3% of people with H pylori infection
- H pylori also have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

Clinical aspects of malignancy

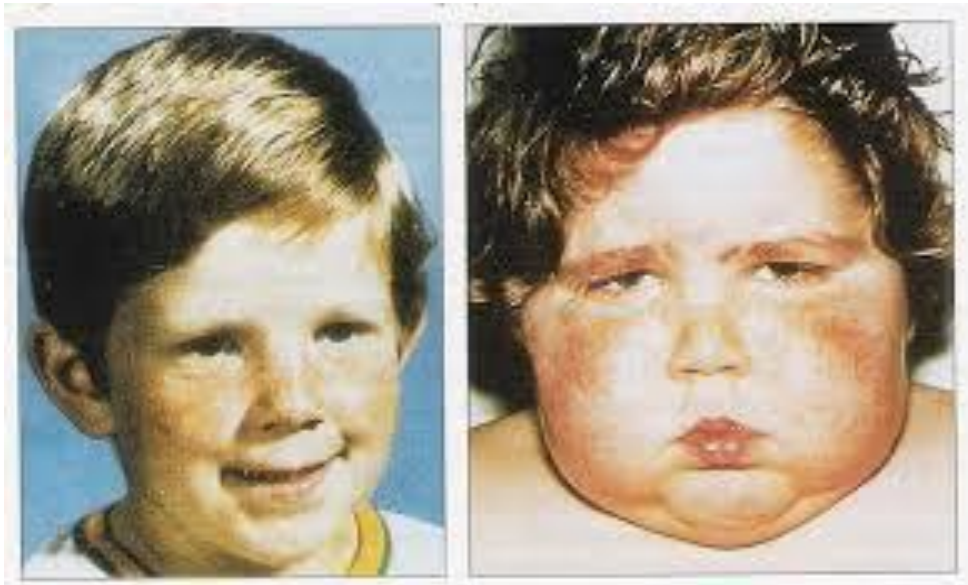
Tumor location

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

Effects of tumors on the host/ location effect

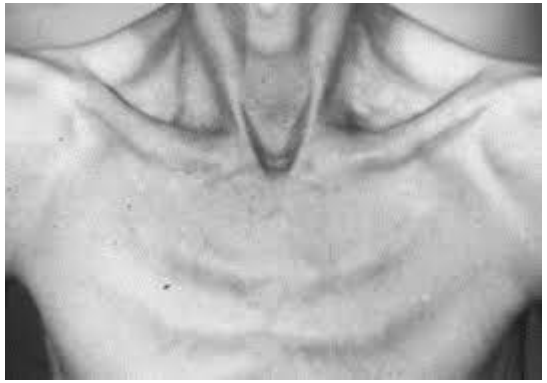


Effects by hormonal secretions
example pituitary adenoma can secrete ACTH and cause Cushing syndrome



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 and muscle wasting**
- **TNF produced from macrophages is probably the main factor for these changes**

- 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

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**

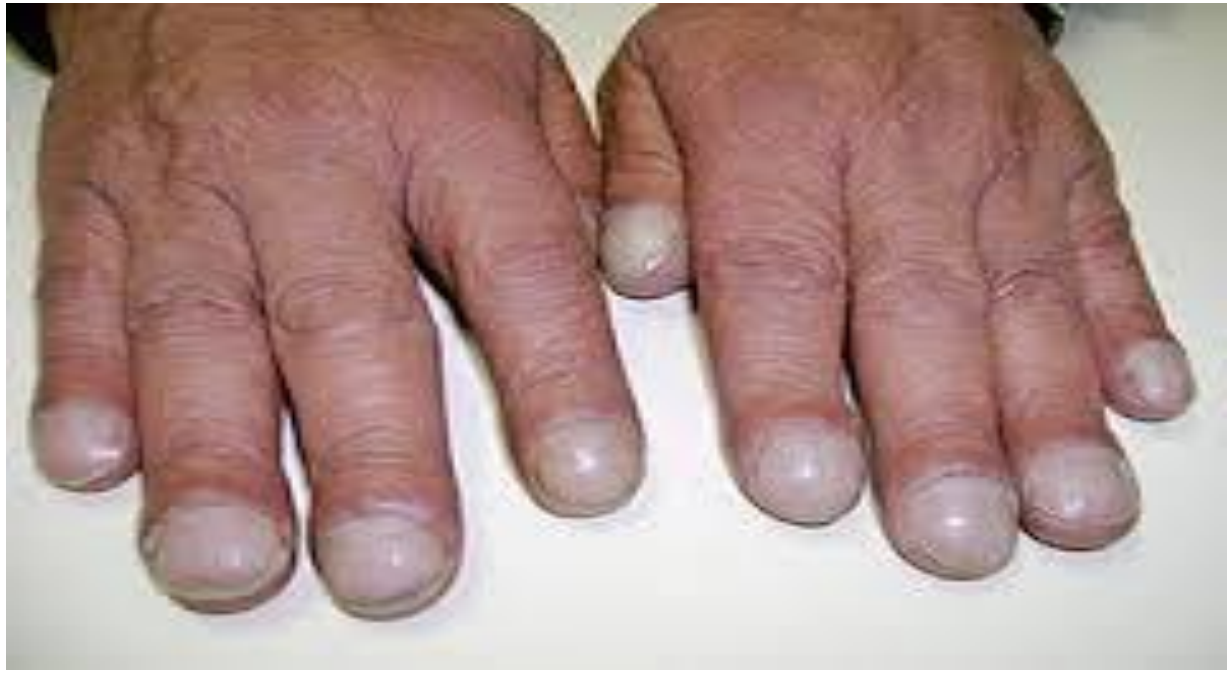
Paraneoplastic syndromes

Table 6.6 Paraneoplastic Syndromes

Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma 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 Breast carcinoma Renal carcinoma Adult T cell leukemia/lymphoma	Parathyroid hormone–related protein, TGF-α
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Ovarian carcinoma	Insulin or insulin-like substance
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	Immunologic
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

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

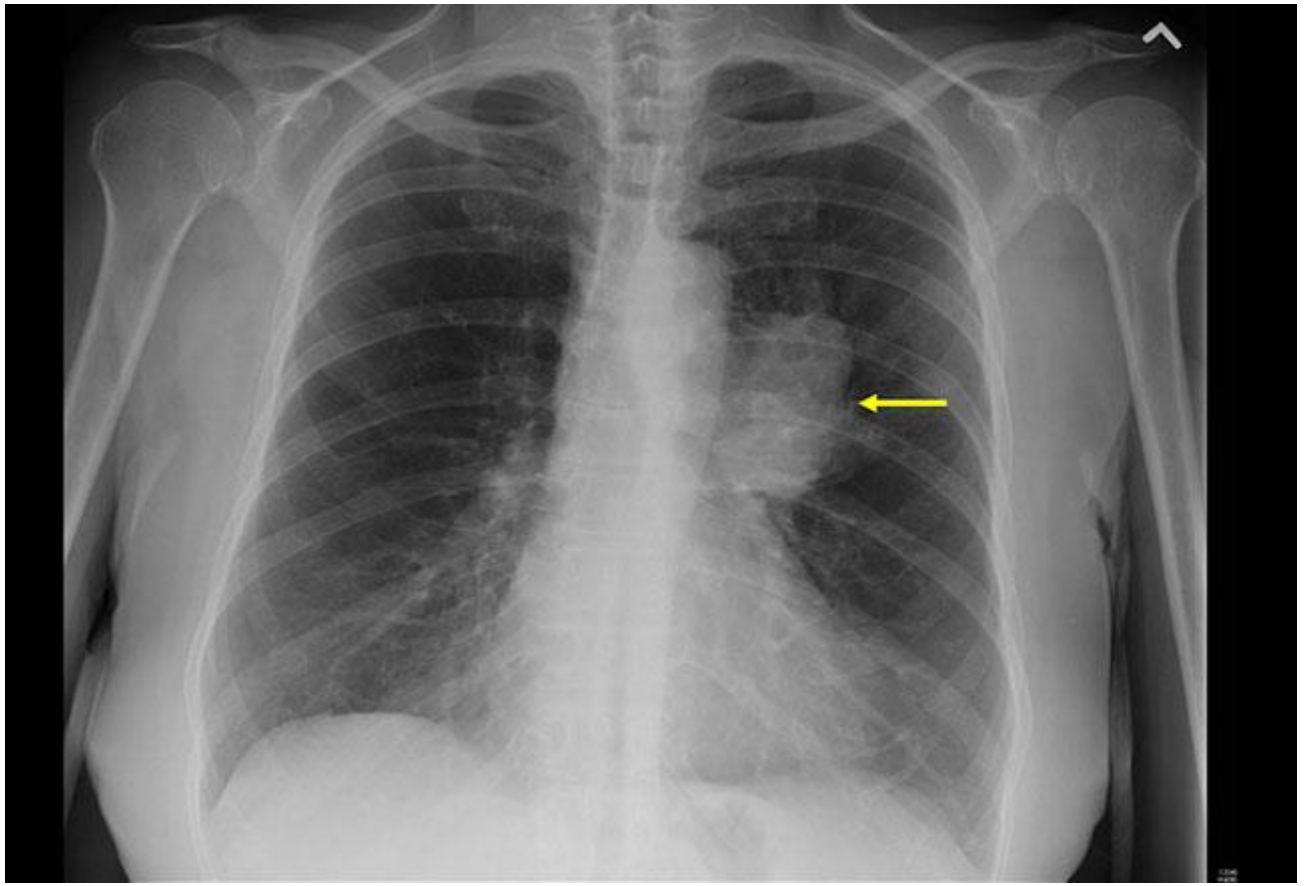
Clubbing of fingers is paraneoplastic, mainly due to lung cancer… etiology is unknown



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

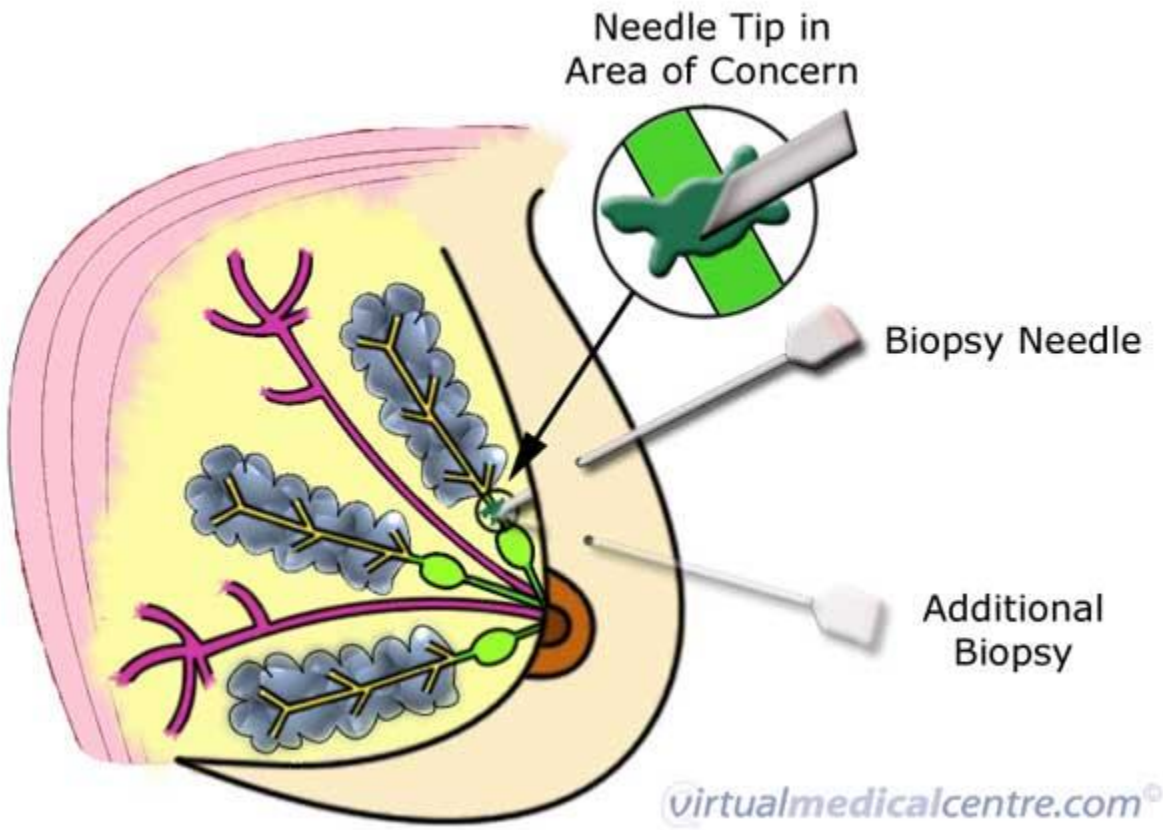
Imaging



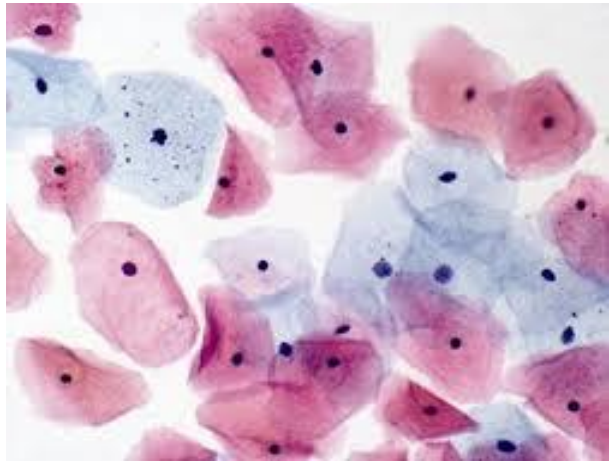
Lab tests/ morphology

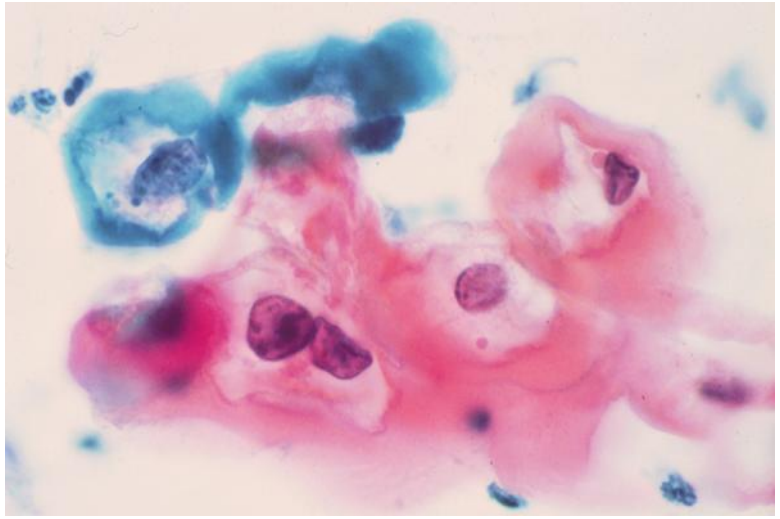
- **Cytologic smear**: cervical smear, sputum..
- FNA= **fine needle aspiration**, if a mass is easily accessible like: breast, thyroid. Or accessible by imaging technique: under imaging guidance FNA can be taken
- **Incisional biopsy**: representative sample taken
- **Excisional biopsy**: all the mass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

FNA.. Breast cancer

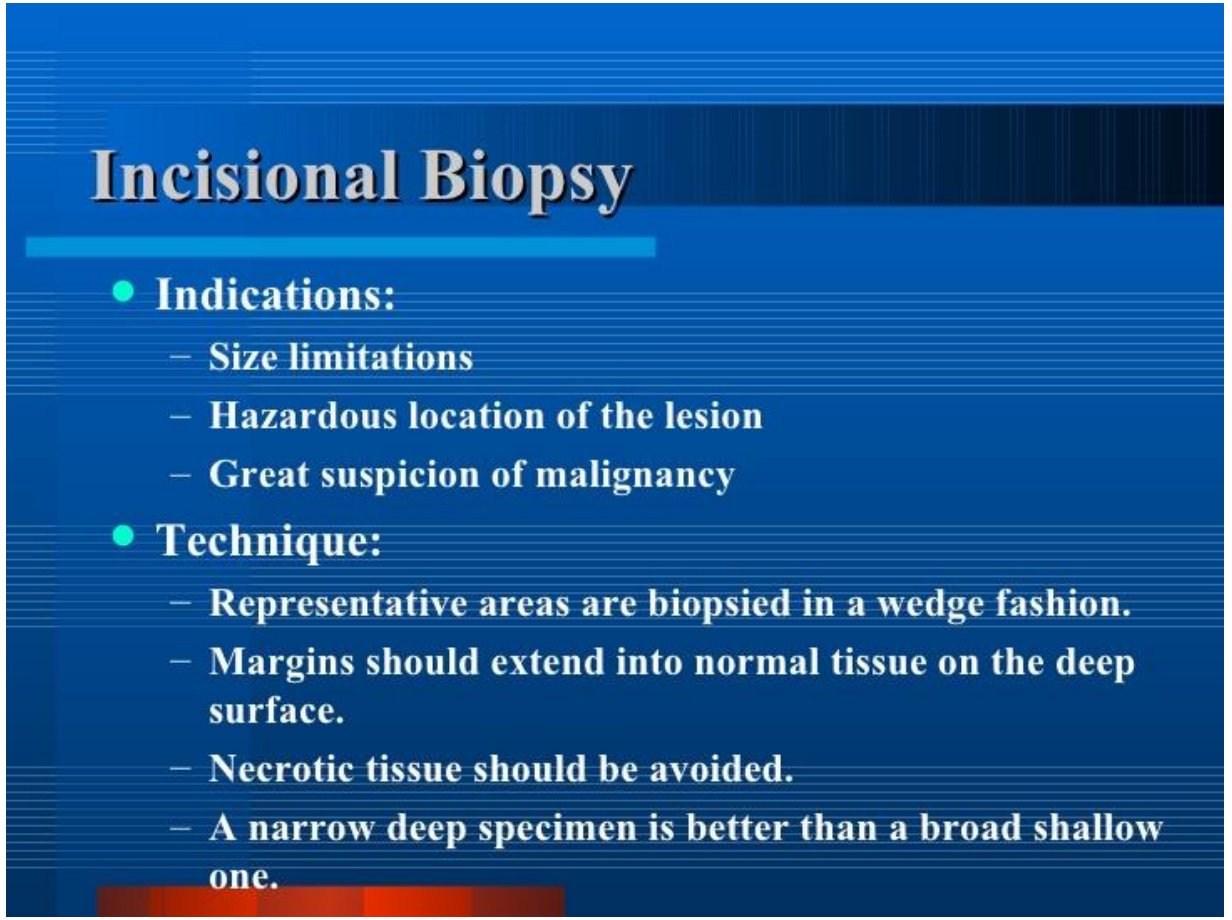


Cytologic smear
= pap smear





Incisional biopsy

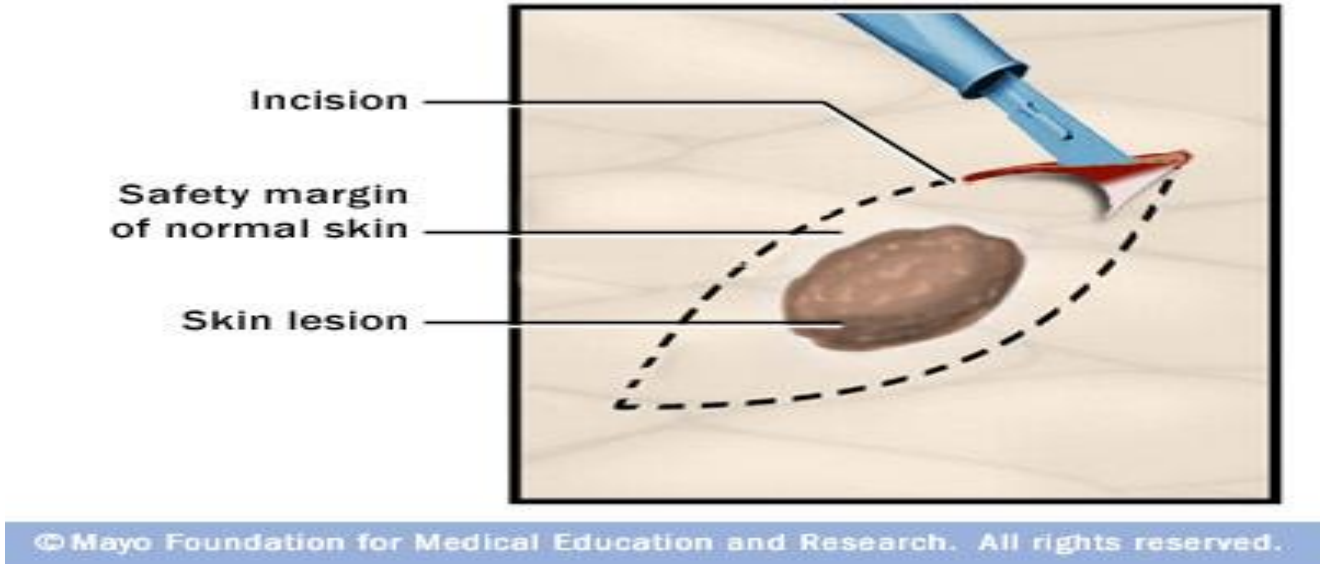


Excisional Biopsy

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



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

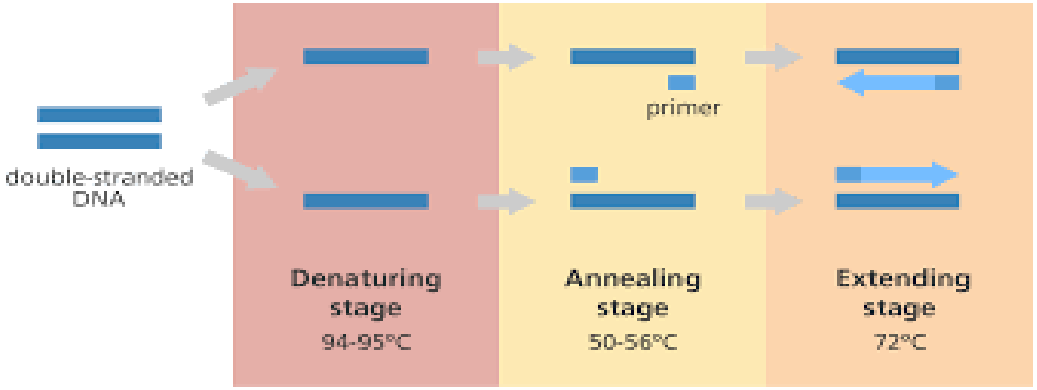
- Used to decide management during the surgery

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