Academic lectures for students of medical schools – 3rd Year updated 2004 - 2015

GENERAL PATHOPHYSIOLOGY

NEOPLASMS 1
CLINICAL PATHOLOGY

R.A.Benacka, MD, PhD
Department of Pathophysiology
Faculty of Medicine, UPJS, Slovakia

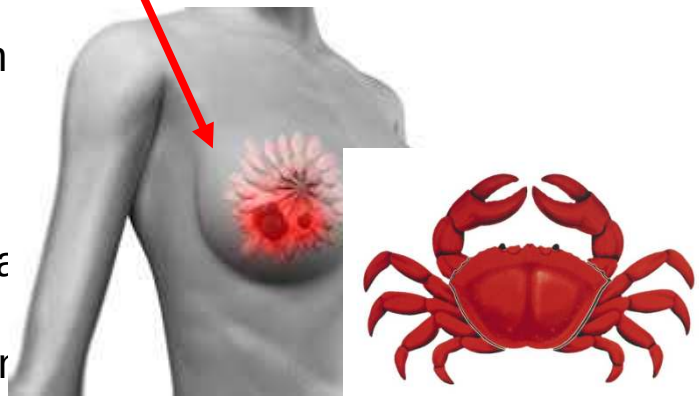
Epidemiology

- Incidency of neoplasms
- Mortality of neoplasms
- Age related types of tumours

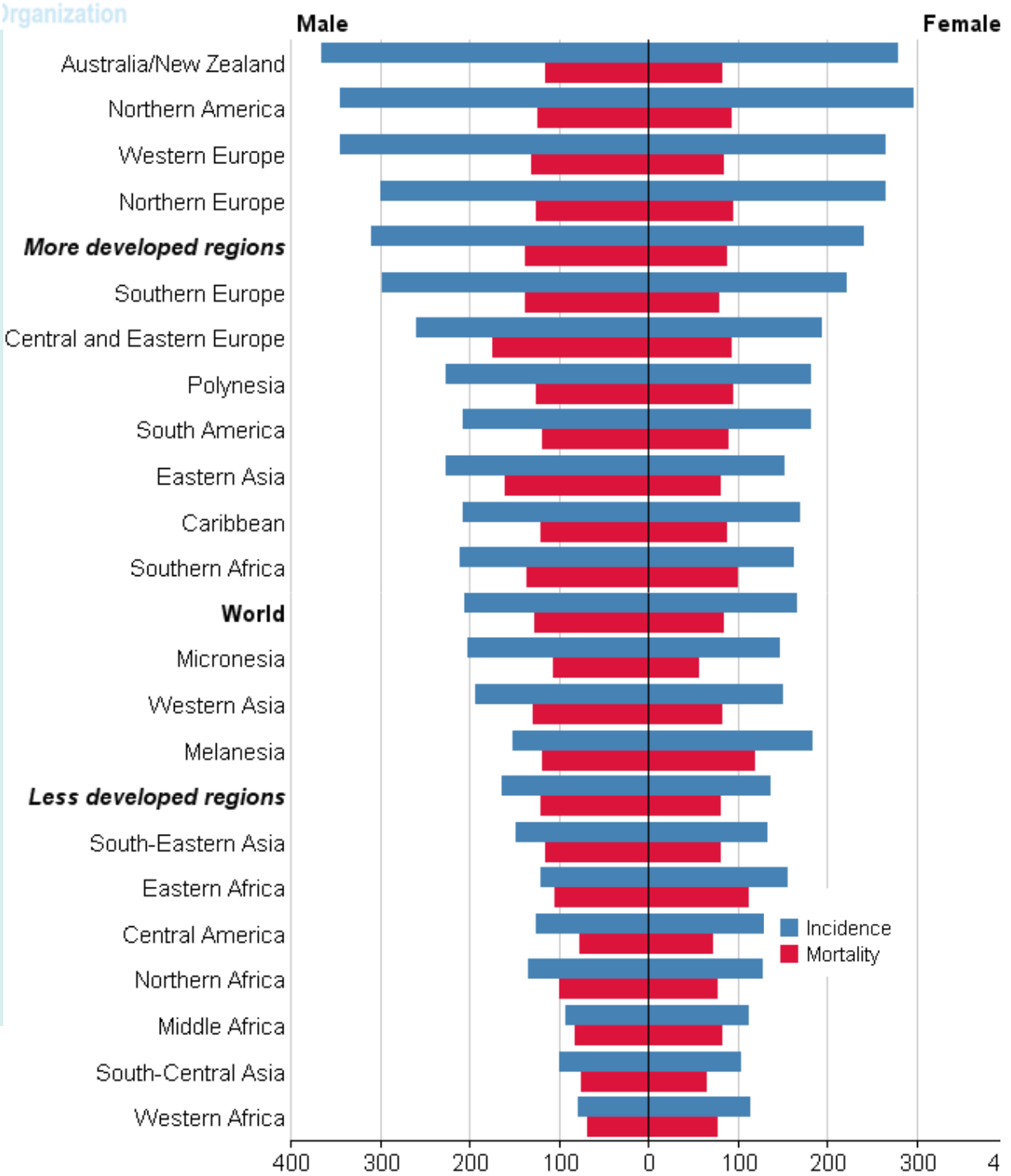
Neoplasms - history

- Evidences of **bone tumors** were found in **prehistoric remains of homo sapiens** and predestors. Description of disease found in early writings from *India, Egypt, Babylonia,* and *Greece*.
- **Hippocrates** distinguished benign from malignant growths; introduced the term ***karkinos*** (in Latin ***cancer***) presumably because a cancer adheres to any part that it seizes upon in an obstinate manner like the crab.
- **Hippocrates described in detail cancer of the breast**, and in the 2nd century AD, Paul of Aegina commented on its frequency.
- Over the decades paleoarchaeologists have made about **200 possible cancer sightings** dating to prehistoric times. The oldest known case of metastasizing prostate cancer was found in Scythian burial mound in the Russian region of Tuva.
- Terminology comes form greek and latin words:
  - **Neoplasia** - the process of "new growth," and a new growth called a neoplasm.
  - **Tumor -** originally applied to the swelling caused by inflammation. Neoplasms also may induce swellings. Non-neoplastic usage of tumor has passed; the term is now equa with neoplasm.
  - **Oncology** (Greek oncos = tumor) - the study of tumors. Car is the common term for all malignant tumors.

Karkinos *was giant crab which came to the aid of the hydra in battle against Hérakles*



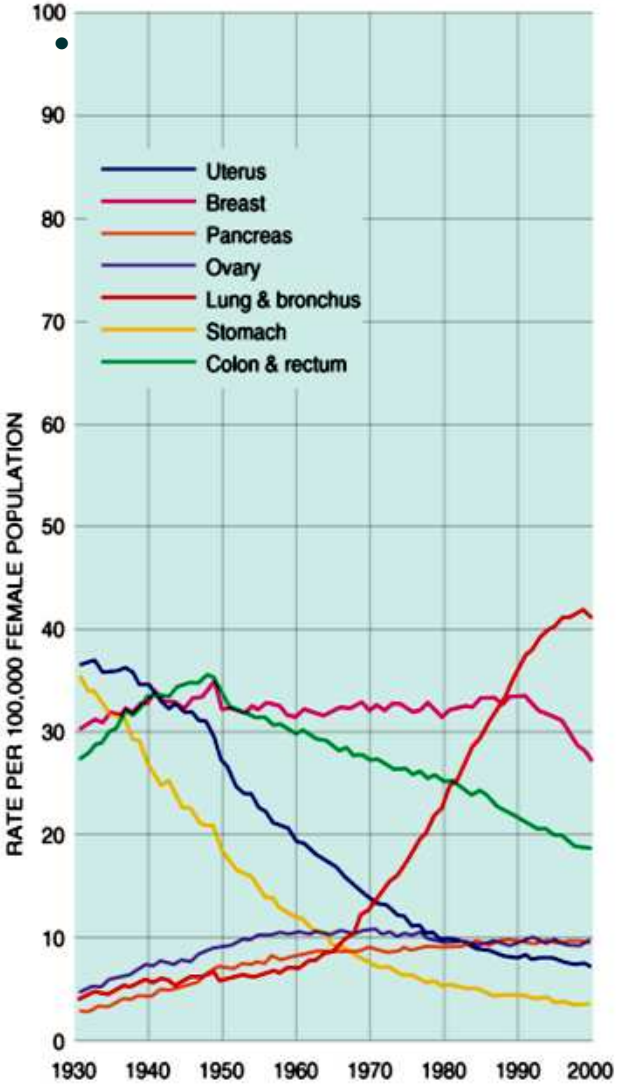
- 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide.
- Incidence in underdeveloped regions not too higher: 57% of new cancer cases, 65% of the cancer deaths
- The overall age standardized cancer incidence rate is **25% higher in men than in women,** with rates of **205 and 165 per 100,000, respectively**. Male incidence rates vary 5x : 79/100,000 in Western Africa to 365/100,000 in Australia. Female incidence varie 3x :103/ 100,000 in South-Central Asia to 295/ 100,000 in Northern America.
- In men, the rates is highest in Central and Eastern Europe (173 per 100,000) and lowest in Western Africa (69).
- In contrast, the highest rates in women are in Melanesia (119) and Eastern Africa (111), and the lowest in Central America (72) and South-Central (65) Asia.

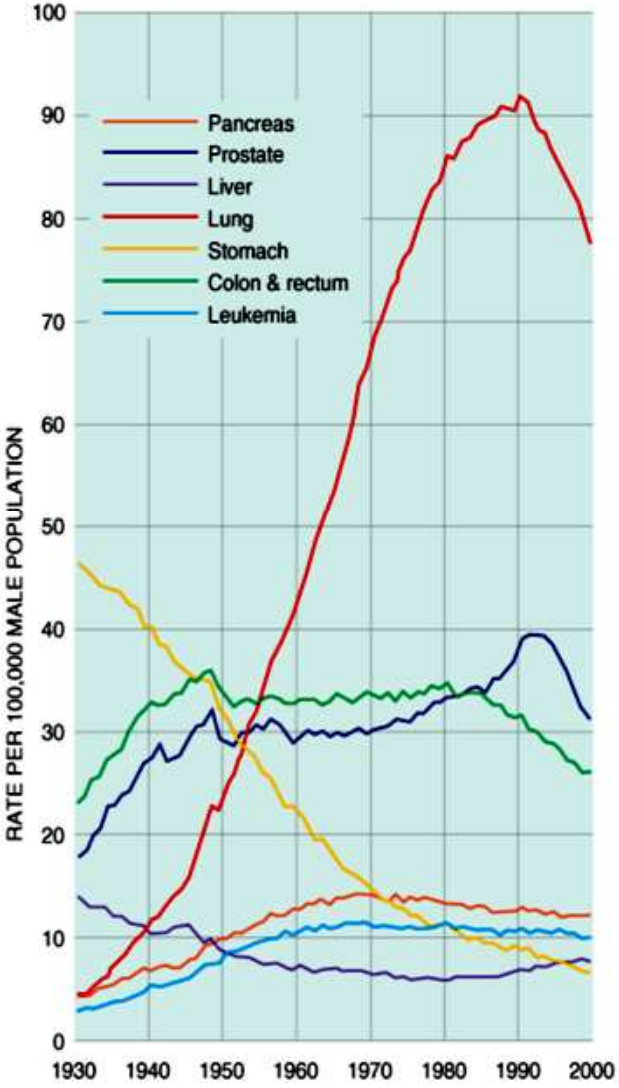


Incidency of neoplasms in US

Conclusions

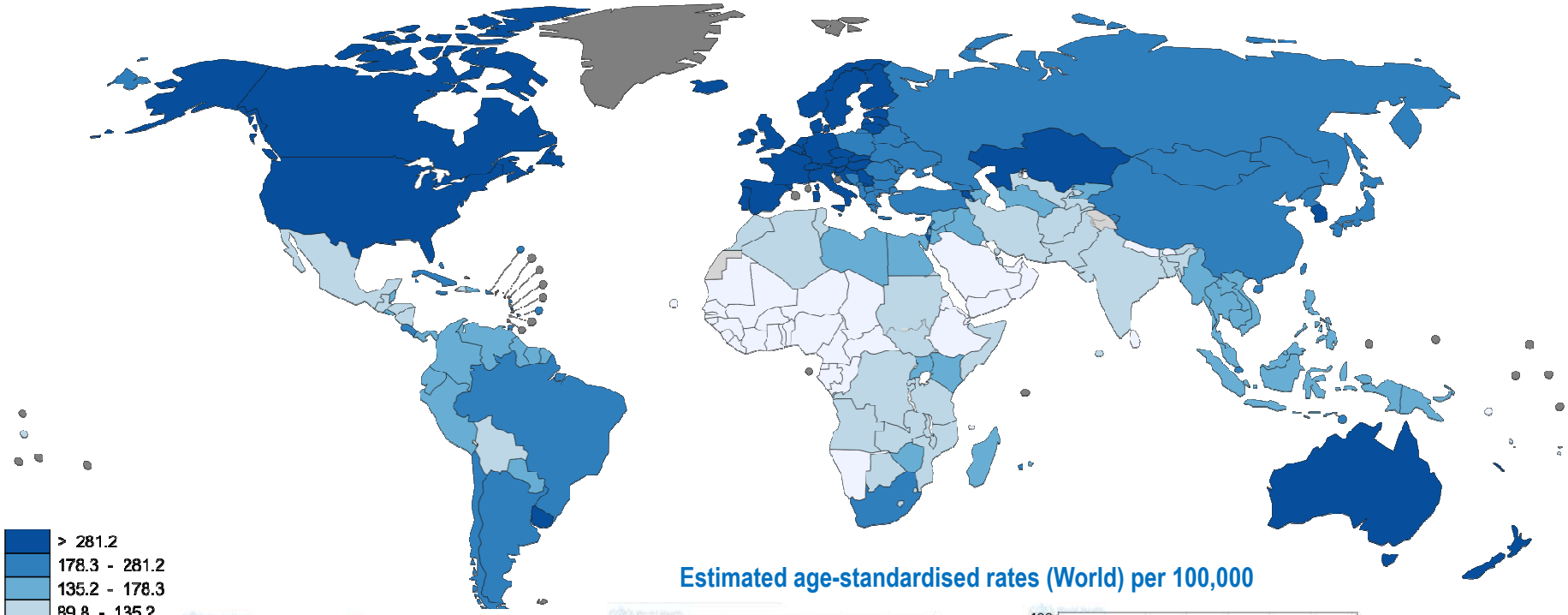
- Incidence of neoplastic disease increases with age. But there are age-related specific tumors
- Overall incidence of cancer increased because of greater longevity in modern times
- In past humans died mostly from infectious diseases, did not live long enough to develop cancers of middle and old age
- Spectrum of cancers remains likely the same over the time
- Occurrence of particular forms of cancer change with age
- Tumors of uterus, stomach, liver decresed over half-century other other like ovary, prostate breast, pancreas remain little changed, tumour of liver and leukemia returned. Lung cancer is clearly on the sustained rise mainly in women.



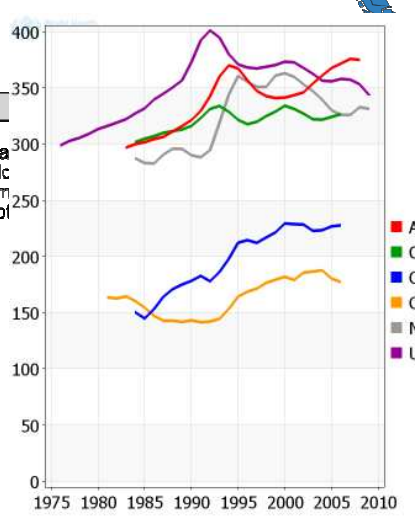


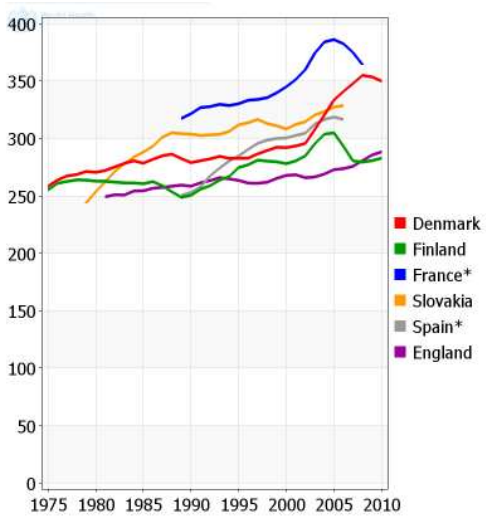
Estimated Cancer Incidence Worldwide : Men

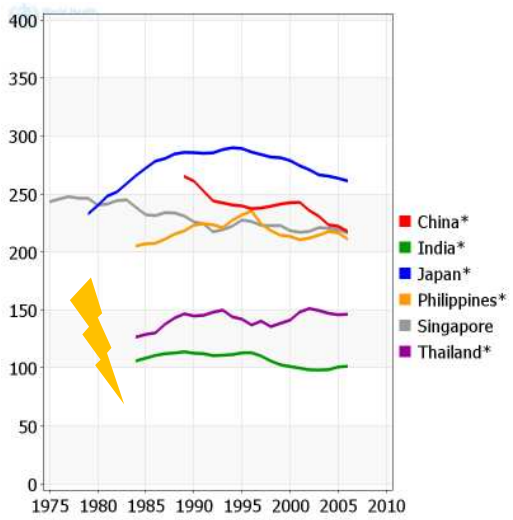
Resource : http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx



Estimated age-standardised rates (World) per 100,000

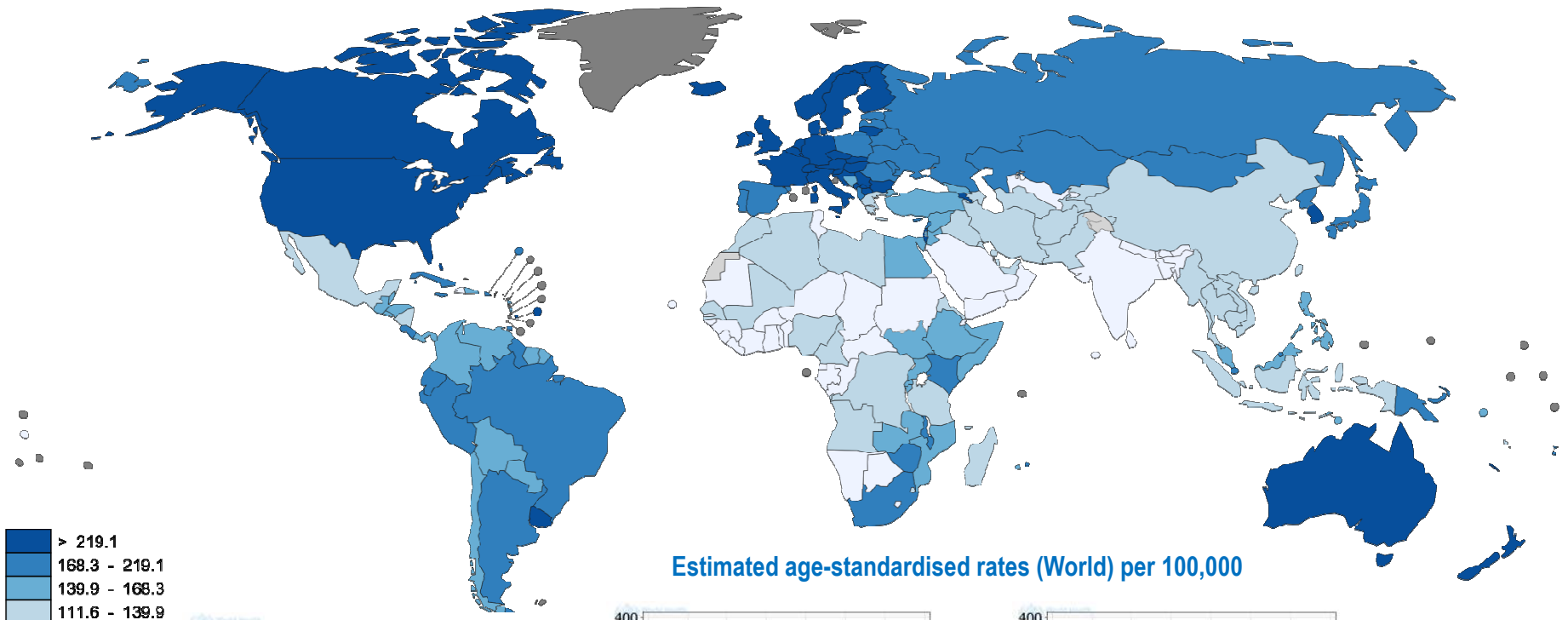




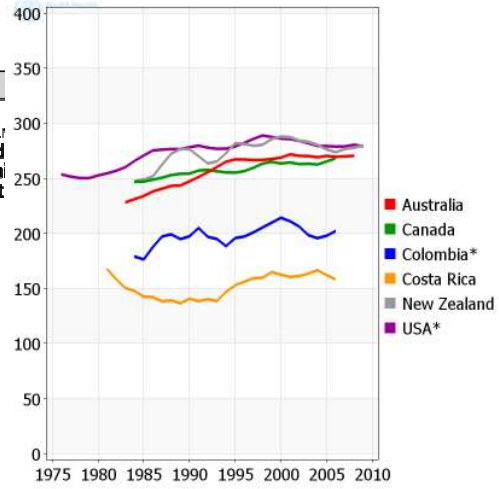


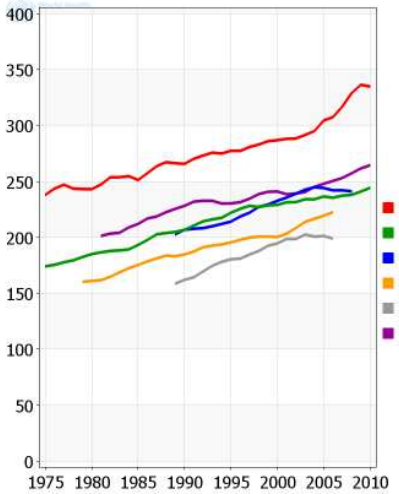
Estimated Cancer Incidence Worldwide : Women

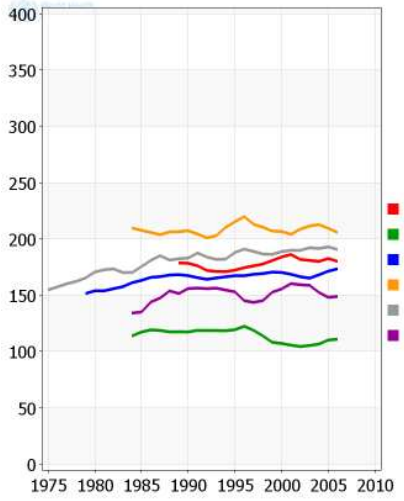
Resource : http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx



The boundaries and nar
on the part of the World
or concerning the delimi
for which there may not

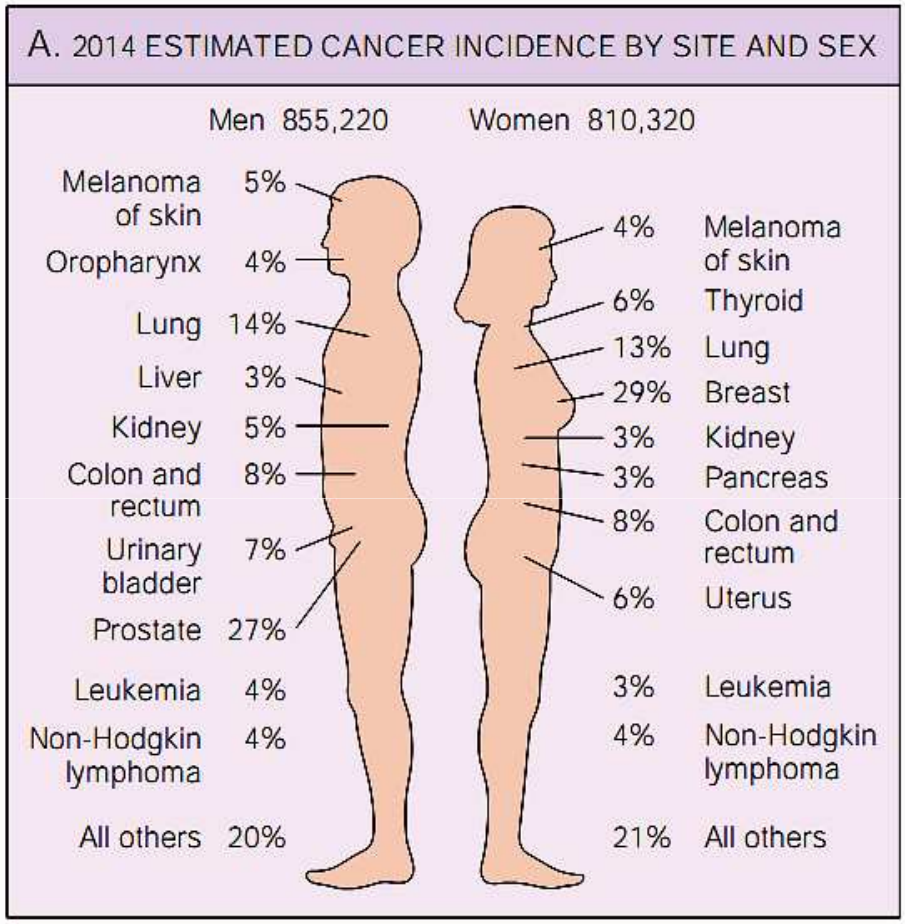


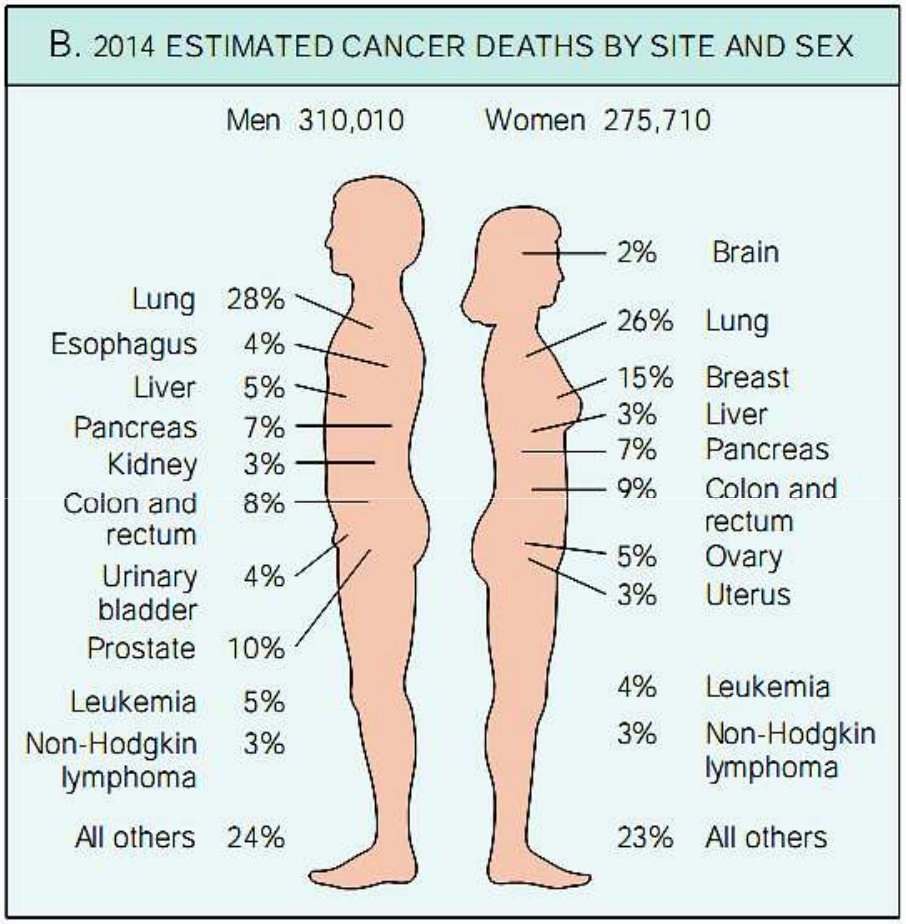




orld Health
ganization

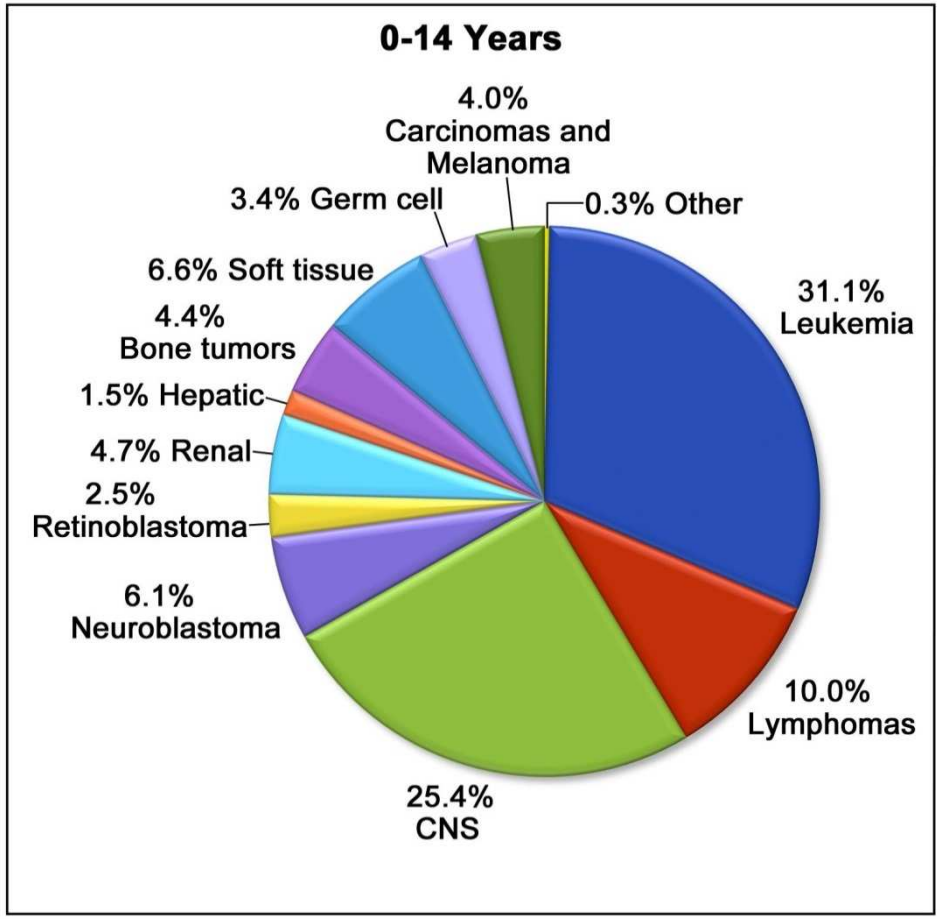
Cancer incidency and death rate by site and sex

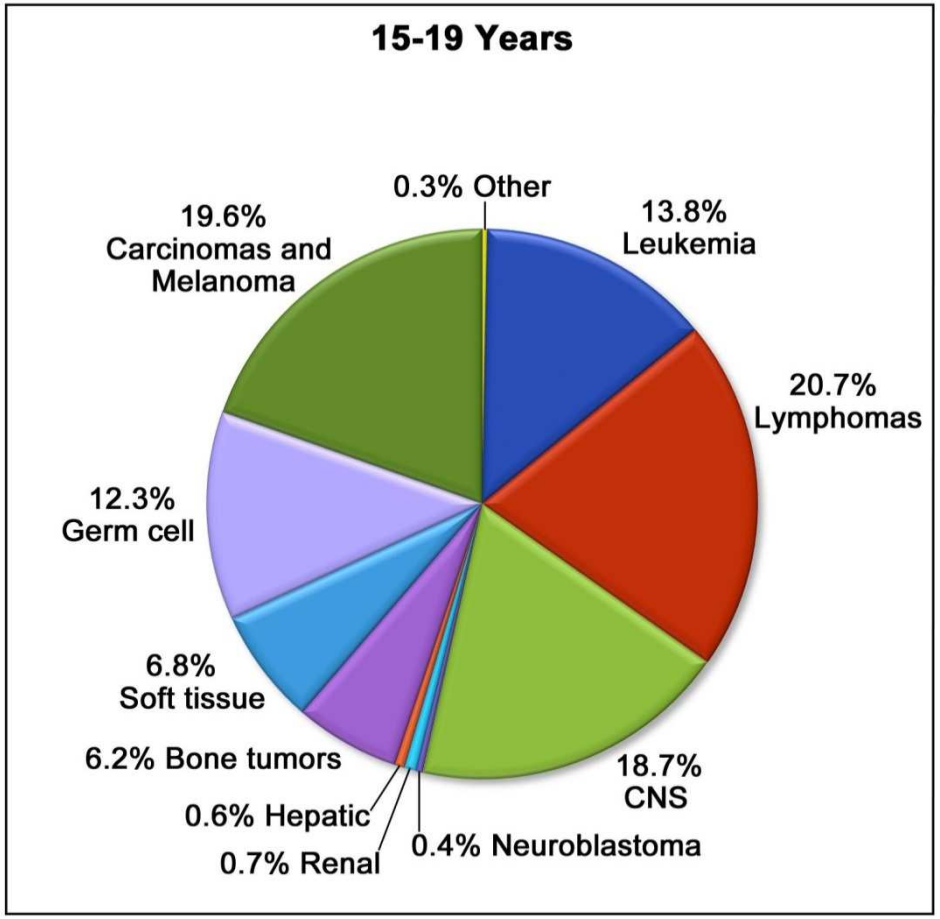




- No increase in age-adjusted cancer death rate in men in the past 50y. Continually decreasing rate in women.
- **Death rate of lung cancer in humans (women and men in average) is ~ 2x higher than any other cancer**
- **The incidence of breast cancer is ~ 2x higher than any other cancer in women; incidence of prostate cancer is ~ 2x higher than any other cancer in men.**

Occurence of tumors before 20th year of life





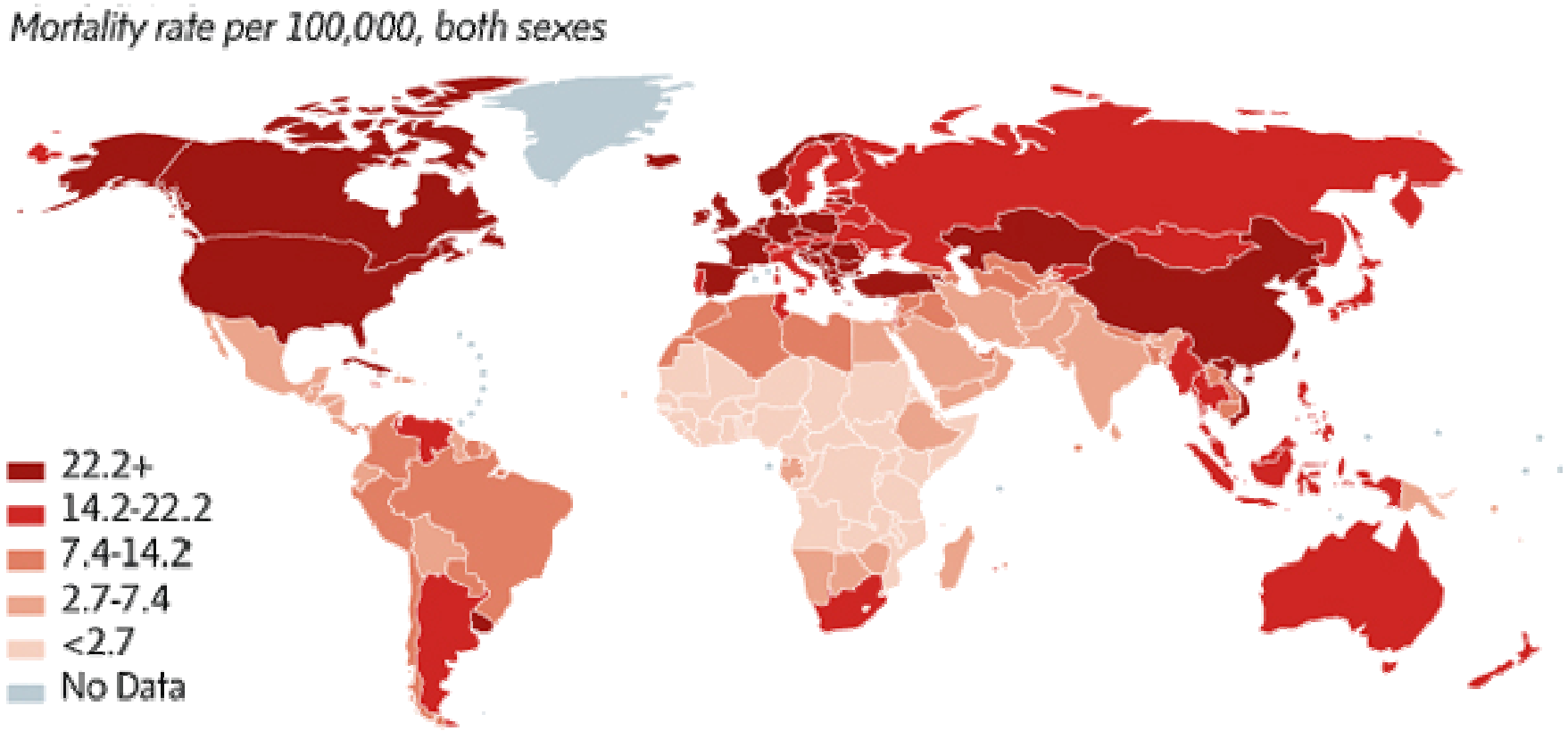
- Up to 40% of tumors in childhood are haematological – leukemias and lymphomas; cca 30 % are tumors of CNS (brain and spinal cord; 6-7% from that is neuroblastoma, kidney tumors 5-6%, tumors of bones 5%, tunmors from muscles (rhamdomyosarcoma) 4%, retinoblastoma 3%.
- Cancer of testes and ovaries represent 13 % in postpubertal age, melanomas and skin carcinoma up to 20%, around 30% are hematological and 19% brain tumors.

International Agency for Research on Cancer

World Health Organization

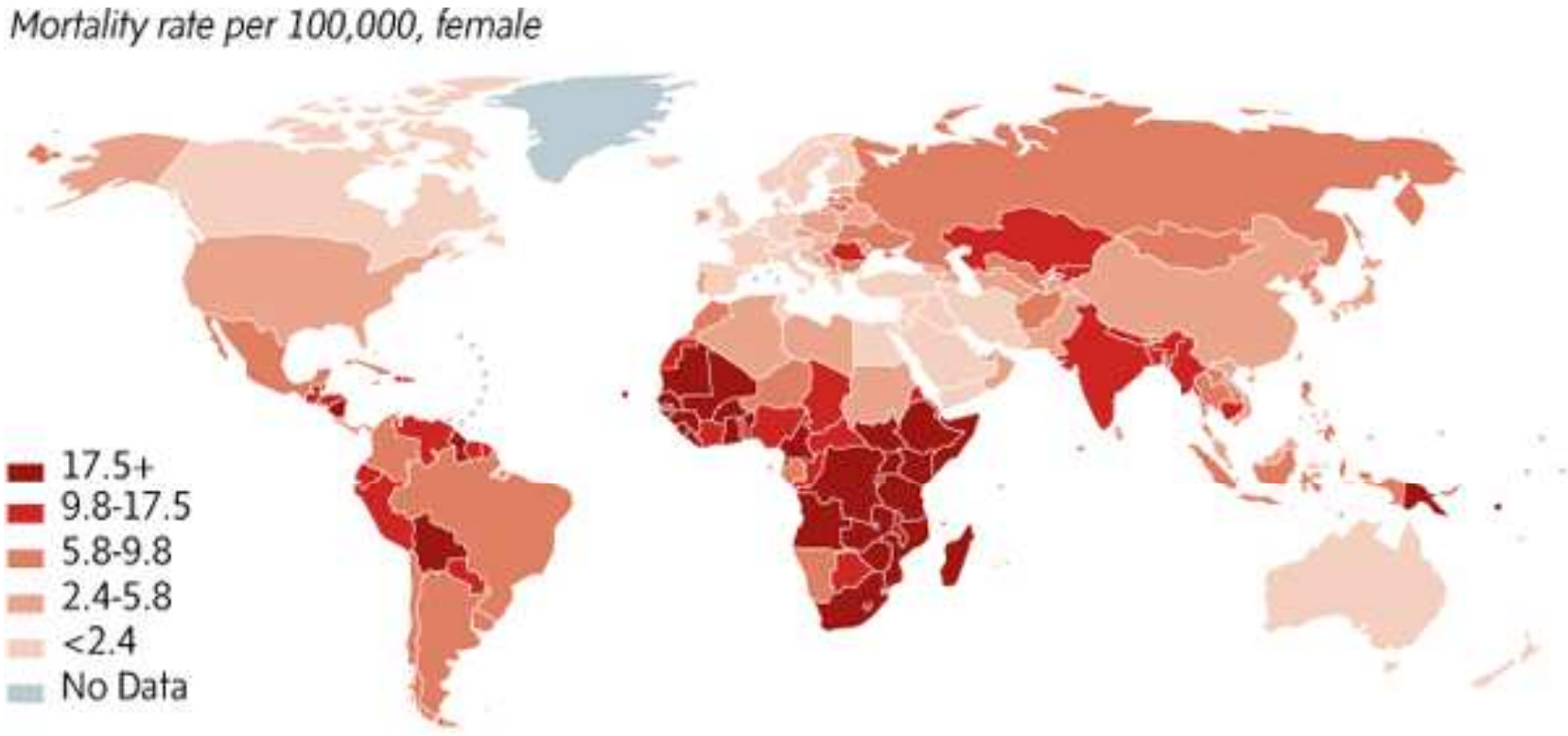
Specific tumors mportality

Lung cancer



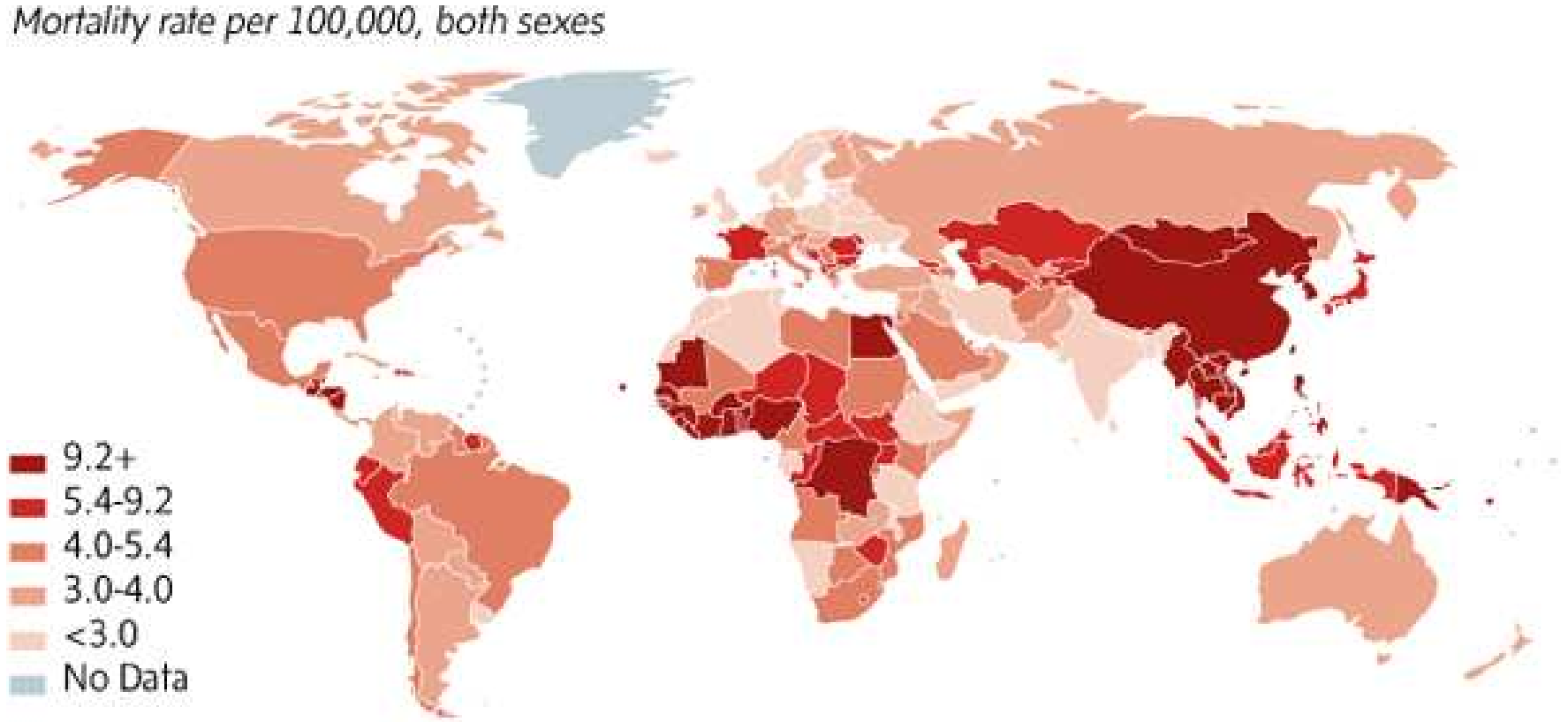
- most common – and deadliest – cancer in the world, with an estimated 1.8 million new cases and 1.59 million deaths in 2012; going up for women and down for men
- smoking rates is highest in Central and Eastern Europe (53.5 new cases per 100,000 people in 2012), and lowest in West Africa (1.7 new cases per 100,000)

Cervical cancer - women



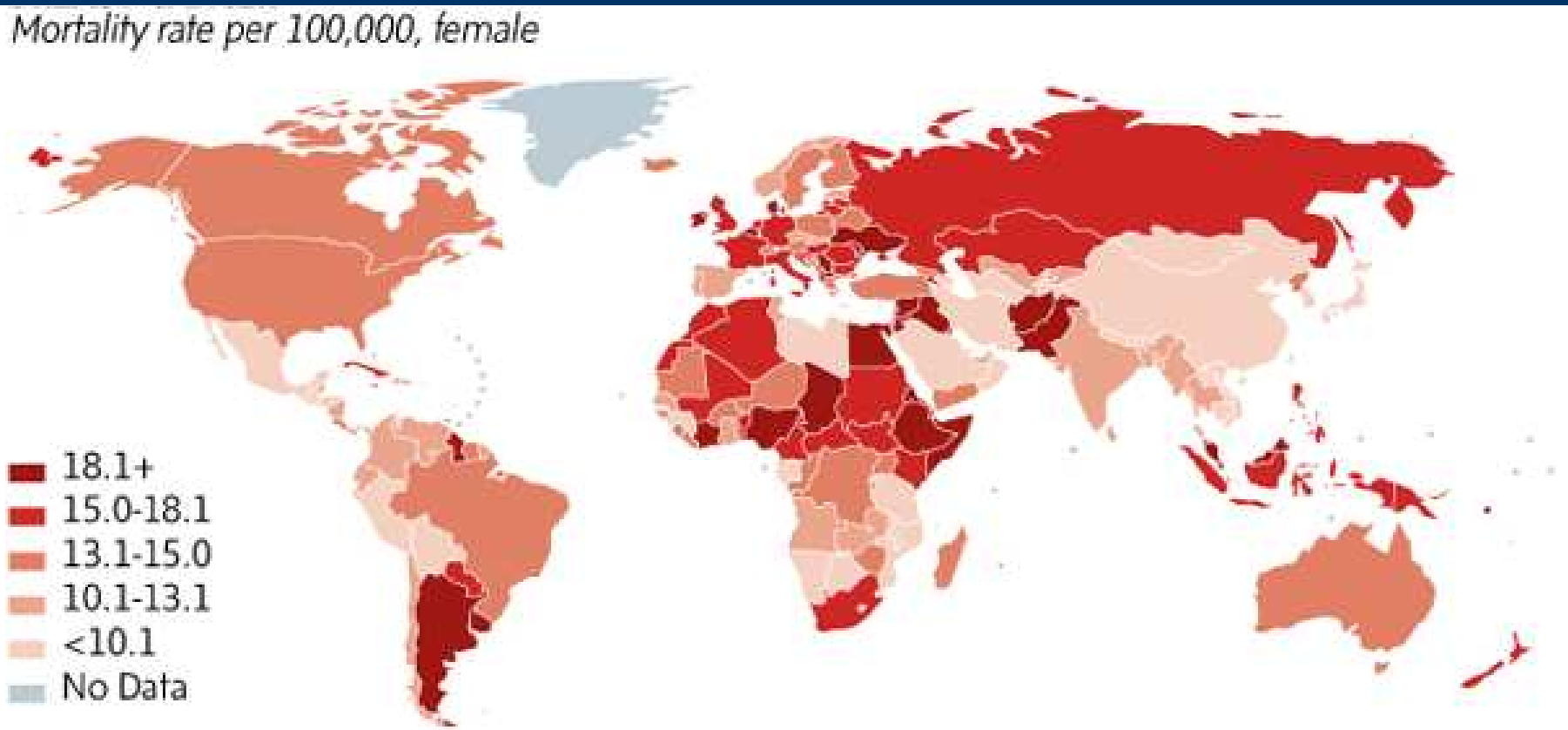
- Fourth-most common cancer in women, with an estimated 528,000 new cases and 266,000 deaths in 2012; women in the developing world show 10x higher death rate ;
- Finland - introduced the best cervical-cancer screening program in the world; human papillomavirus, or HPV vacination

Liver cancer



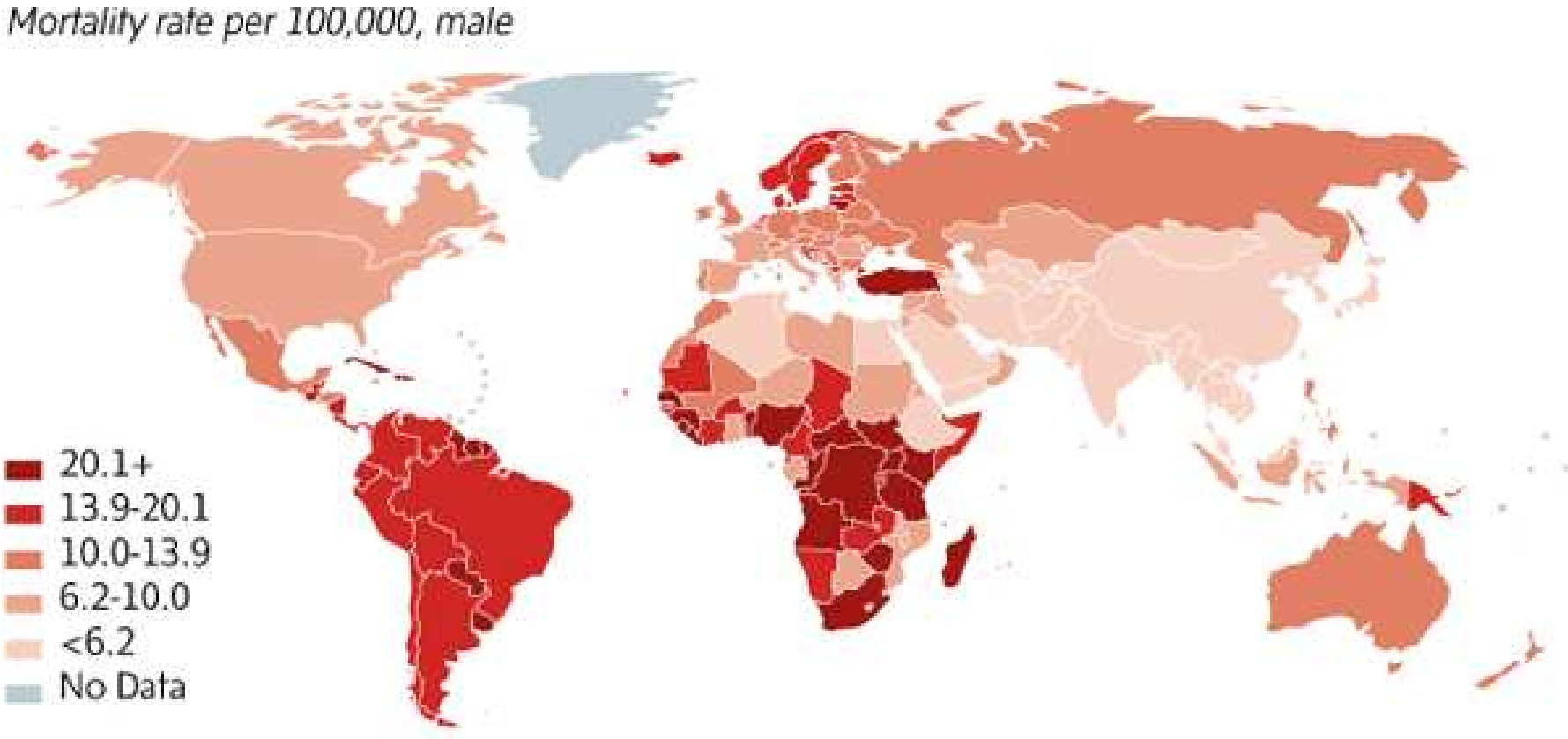
- Second-most common cause of cancer death around the world; associated with hepatitis B, alcohol
- Asia - Mongolia, Laos, Vietnam, Cambodia, Thailand and China top 10 countries for liver-cancer deaths, Mongolia - highest cancer mortality rate of any country (161 deaths per 100,000 people)
- Hepatitis B vaccination program after birth in China; Canada logged 3.6 new cases of liver cancer and 3.3 deaths per 100,000 people in 2012.

Breast cancer - women



- The most common cancer in women (1.7 million new cases in 2012 and 522,000 deaths); 1,8 million new cases in 2015 and 423,000 deaths = decrease 5 % over 10 years
- Increased 20 % since 2008: perfect diagnostics in Europe (90 new cases per 100,000 women); no screening in East Africa (30 per 100,000 women) weak screening in Asia (42 per 100,000 women) ;
- The highest proportion in Western Europe – Belgium, Denmark and France; highest mortality rates in Fiji, Bahamas and Nigeria

Prostatic cancer - men



- The most frequently diagnosed cancer among men ~ 88.9 new cases for 100,000 men; 3rd in mortality: ~ 9.4 per 100,000 North America and ~ 8,3 per 100,000 in Europe
- Prostate-specific antigen (PSA) blood test has made early detection and treatment
- Aggressive testing campaigns have raised concerns that prostate cancer is being overly diagnosed
- Prostate cancer is deadlier in Caribbean men (29 per 100,000 men) and sub-Saharan Africa (24 per 100,000 men)

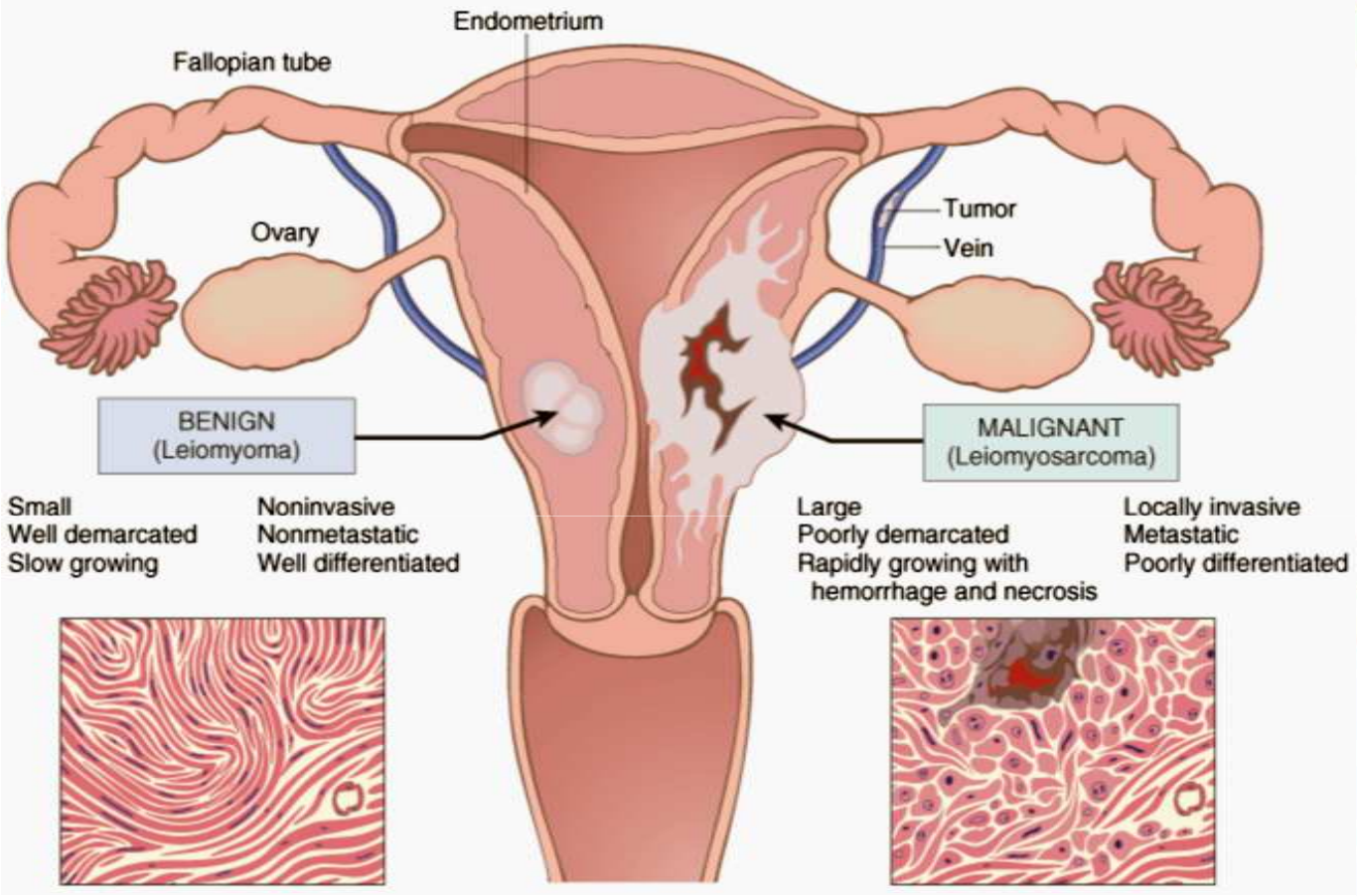
Characteristics of the tumor cells

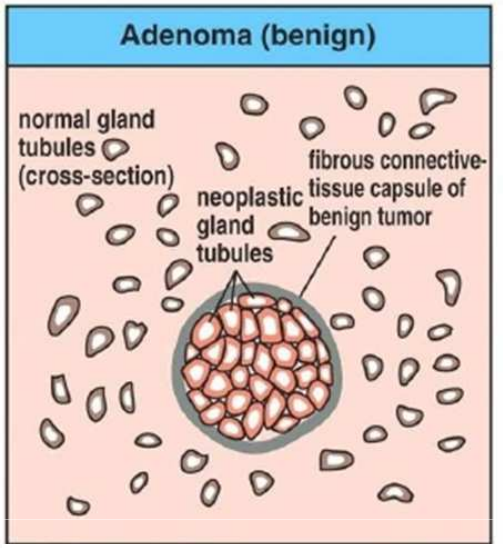
- Benign tumors
- Malignant tumors

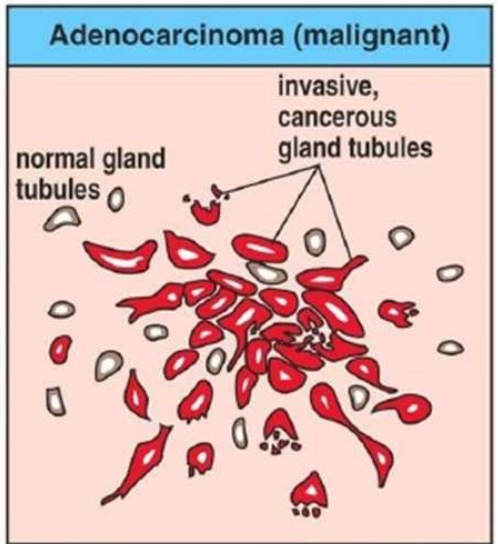
General considerations

- Tumors are **genetic,** mostly **non-hereditary disorders**, which develop due to **specific mutations** in the **specific genes** of the somatic cells (less commonly in germ cells). These specific genes those regulating **cell growth (cell cycle movement in response to mitogenic signals, DNA repair and apoptosis)** Tumorigenic mutations must render them the capacity **to grow and multiply in excess of other cell,** and to do that **autonomously**, irrespective of body needs.
- **Not every mutation in above genes is tumorigenic (neoplastic**); actually, most of them are out of effect or, on contrary, they induce degradation, or atrophy
- Neoplasms are derived from **cells that normally maintain a proliferative capacity** (i.e. mature neurons and cardiac myocytes do not give rise to tumors). In general, **neoplasms are irreversible.**
- **Tumors do not develop overnight;** it **is mutlistep long-term progress**. Unfortunately, we are not aware of that, only in time when tumor is manifested clinically, i.e. when tumor contains ~ 10^9 cells. Tumorigenesis may be common.. Many tumors are eradicated by immunological surveilance
- A **tumor may express varying degrees of differentiation**, from relatively mature structures that mimic normal tissues to a collection of cells so primitive that the cell of origin cannot be identified.
- The stimulus **(exact reason)** responsible for the uncontrolled proliferation may not be identifiable; in fact, it is not known for most human neoplasms.
- All tumors are typical by **overgrowth`forming local mass, and either non invasive growth respecting the borders and surroudung structure or invasive growth – outgrowing of finger like processes in star like appearance**

Comparison of benign and malignant tumors







Benign and malignant tumours

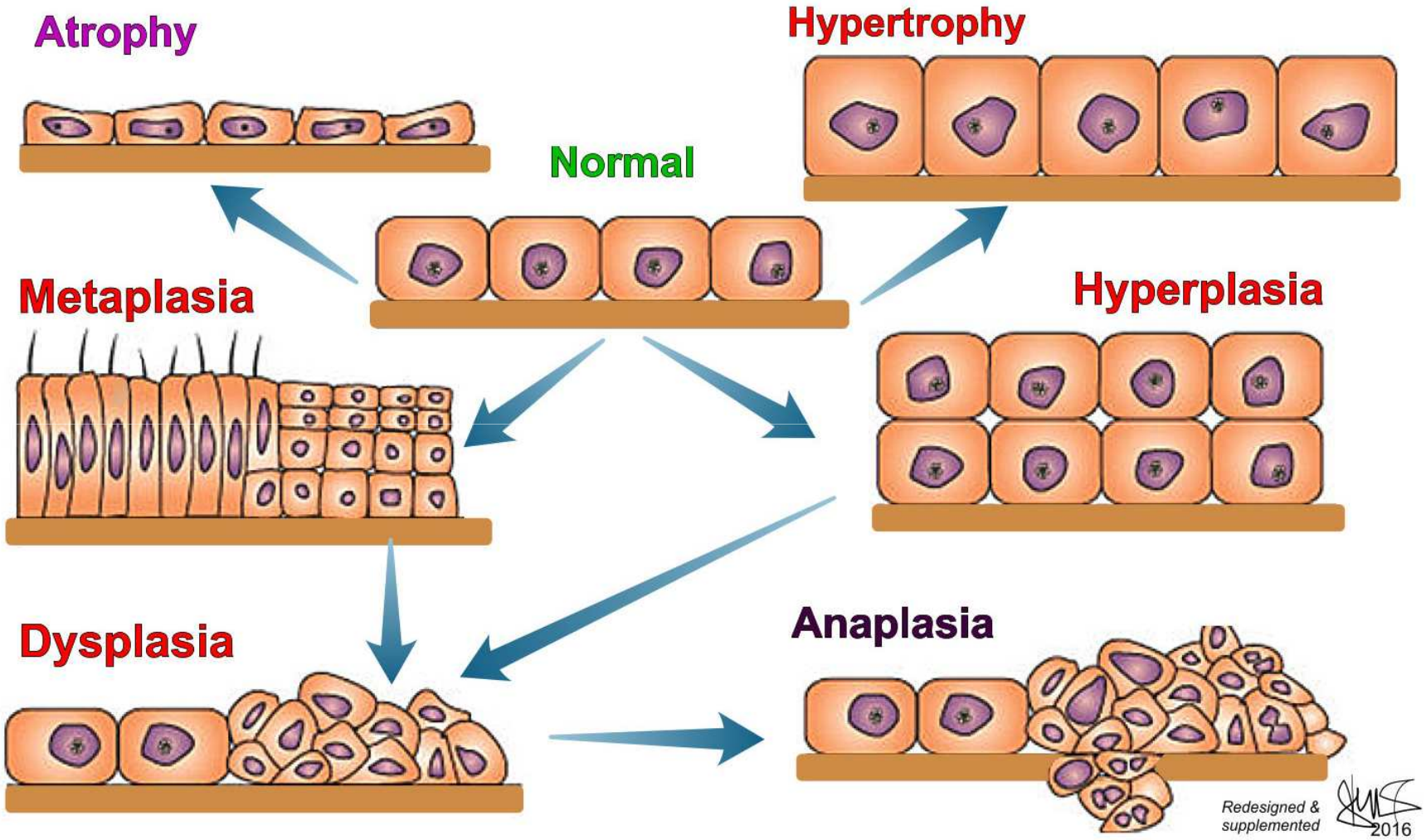
BENIGN TUMORS

- **Benign tumors** are **histologically similar to their tissues of origin, their growth is slow**
- The gross structure of a benign tumor **may depart from the normal and/or papillary or polypoid configurations** (papillomas of the bladder and skin and adenomatous polyps of the colon).
- Benign tumor are **inable to invade** into adjacent tissue and **inable to metastasize.**
- Benign tumors are circumscribed by a connective tissue **capsule**, many benign neoplasms **are not encapsulated** (papillomas and polyps, hepatic adenomas, many endocrine adenomas, and hemangiomas.

MALIGNANT TUMORS

- Malignant neoplasms **range from well differentiated types into undifferentiated ones**, ***well-differentiated cancer*** evolves from maturation or specialization of dedifferentiated cells as they proliferate
- ***undifferentiated malignant tumor*** **(anaplastic)** derives from proliferation without complete maturation of the transformed cells.
- Malignant tumors are **able to invade** into adjacent tissue and **able to metastasize**
- Many cancers arise from stem cells that are present in all specialized tissues and do not represent "reverse differentiation" of mature normal cells

Changes in cell phenotype towards a cancer



Hyperplasia (proliferation of normal cells)
Metaplasia (conversion in cell type)
Dysplasia (change in cell or tissue phenotype)

Prosoplasia (gain in new cell functions; rediferentiation)
Anaplasia (loss of structural differentation: dediferentiation)
Neoplasia (abnormal rate & cell proliferation)

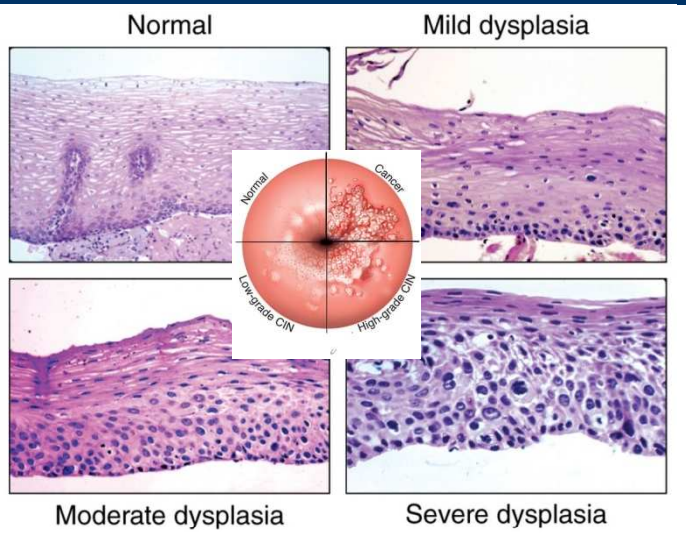
Pre- malignant changes

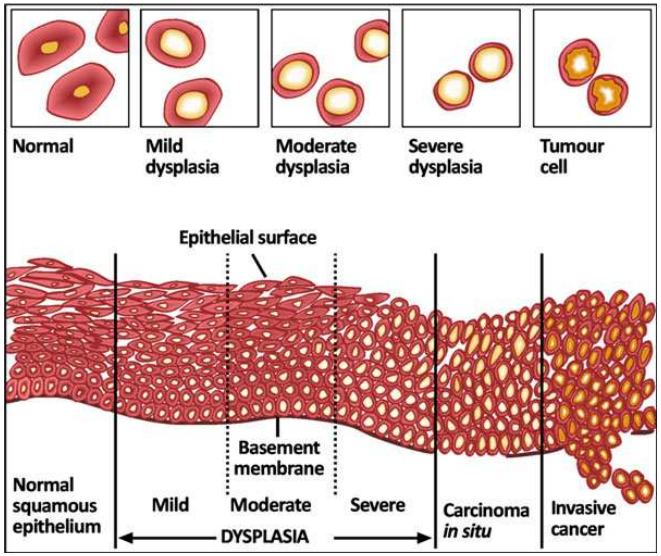
METAPLASIA reversible replacement of one differentiated cell type with another **mature differentiated cell type** more suited to the new environment

- part of normal maturation process or caused by some sort of abnormal stimulus.
- secretory columnar epithelium with stratified squamous epithelium **(squamous metaplasia)**

DYSPLASIA - expansion of immature cells, with a decrease in the number and location of mature cells. Indicative of an **early neoplastic process**

- epithelial dysplasia of the **cervix** (cervical intraepithelial neoplasia) – detected by an abnormal pap smear) an increased population of immature (basal-like) restricted to the mucosal surface, vaginal intraepithelial dysplasia, vulvar intraepithelial dysplasia.
- **Myelodysplastic syndromes,** or dysplasia of blood-forming cells, show increased numbers of immature cells in the bone marrow, and a decrease in mature, functional cells in the blood.



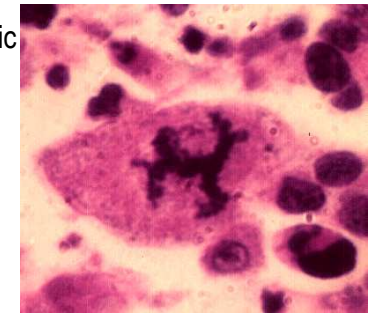


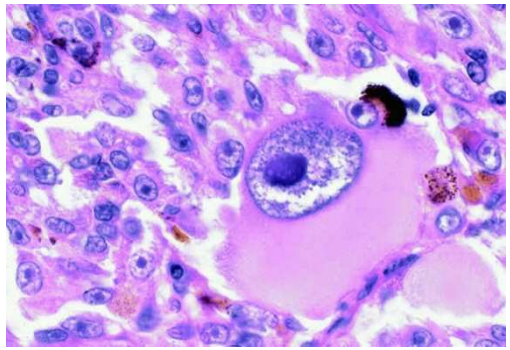
Cell changes from premalignancy to malignancy

ANAPLASIA ("to form backward„) = reversion from a high level of differentiation to a lower level malignant cell community with derepressed undiferentiated cells showing phenotypical and genetic heterogenity. It is marked by a number of morphologic changes:

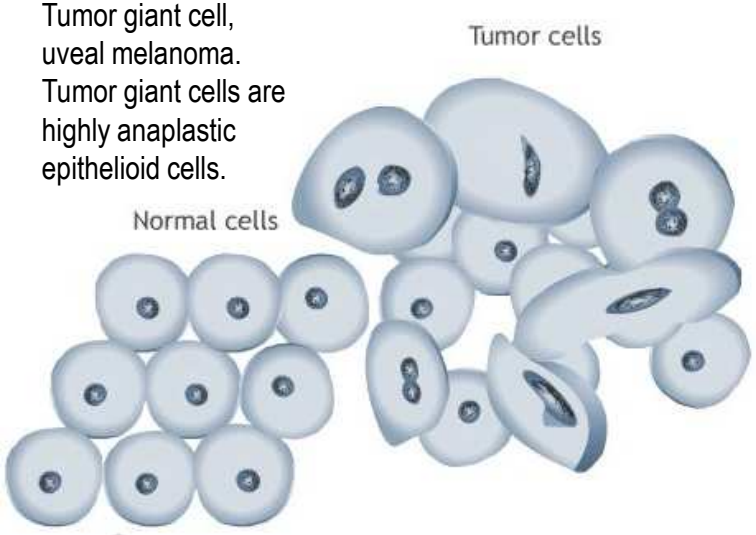
- **Pleomorphism =** variation in size and shape of the cells and the nuclei (many times larger or extremely small and primitive appearing)
- **Nuclear abnormalities** = shape varies from cell to cell, chromatin is often coarsely clumped, distributed along the nuclear membrane, nuclei are of varianle size; nucleus-to-cytoplasm ratio may approach 1:1 (instead of the normal 1:4 or 1:6)
- **Large numbers of mitoses -** some well-differentiated malignancies and most of undifferentiated tumours show higher mitotic rate (mitoses does not prove a tumor: 1. normal tissues with rapid turnover (bone marrow); 2. non-neoplastic - hyperplasias
- **Atypical, bizarre mitotic figures -** tripolar, quadripolar, or multipo-lar spindles; (most important morphol. feature of malignancy)
- **Loss of polarity** = disorientation; masses of tumor cells grow in an a
- **Anaplastic tumor giant cells** = some possessing only a single large polymorphic nucleus and others having two or more Bizarre mitotic hyperchromatic nuclei

Bizarre mitotic figure with multipolar spindle





Tumor giant cell, uveal melanoma. Tumor giant cells are highly anaplastic epithelioid cells.



International Agency for Research on Cancer

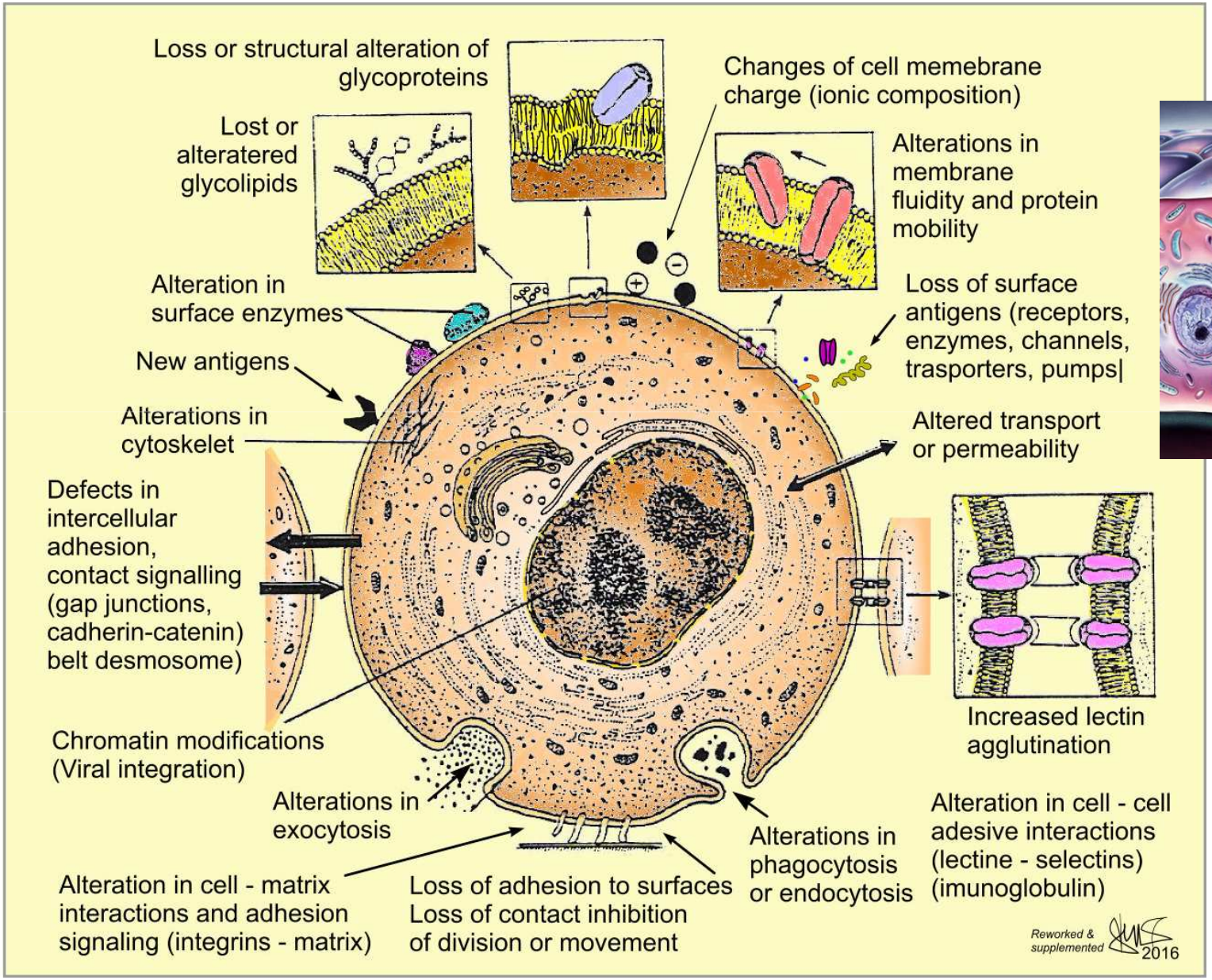
World Health Organization

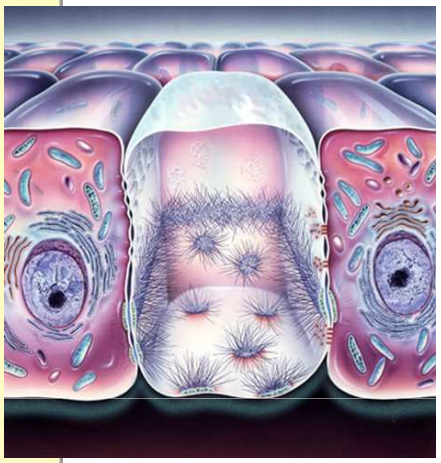
Characteristic alterations in tumor cells

Functional changes in tumor cells

- **Loss of adhesion contacts to other cells and support tissue (loss of ADCG)**
- **Alterations in surface charge** - changes in content of polysaccharides, increased lectin adhesivity
- **Tumours show alteration in weak cell** - cell adesive interactions (lectine - selectins)
- **Loss of gap junction** = break of intercellular signalling between adjacent cells; cooperation, synchronisation
- **Defects in intercellular adhesion** = freeing of cells, independence; defective tight junctions and cadherin-catenin system; desmosome = is typical feature of malignant tumors and the condition for invasive growth
- **Loss of adhesion to surfaces** = loss of integrin to collagen (basement membrane) adhesions
- **Loss of contact inhibition of division and Loss of contact inhibition of movement** typical feature of invasive cancer ; breaking rules of ADCG (anchorage dependent cell growth) cell in dish grow into monolayer, than stop growing; cells in malignancy grow one over another not in monolayer
- **Changes in membrane, superfitial antigens and molecules**
- Alteration or loss of normal ones and presence of new ones (receptors, transporters, channels, etc)
- Loss or structural alteration of glycoproteins and also glycolipds occur in neoplasms
- Alterations in membrane fluidity and protein mobility
- **Alteration in surface enzymes**
- **Alterations in exocytosis, phagocytosis or endocytosis** can occur commonly in neoplasms; especially in leukemic granulocutes, adenomas and adenocarcinomas
- **Alterations in cytoskeletal system** is common in invasive and metastazing cells – necessary reconstrction of cell shape during ameboid movemnt through basement memebrane or diapedesis into and out of vessels
- **Formation of new clones of cells** – in addition to visual difference in cells (pleomorhism), cells in malignant tumor differ by capabilities, expression of different proteins,
- **Chromatin modifications** are very common in anaplasia (condensation of chromatin; abnormal mitottic figures)

Cell alteration in tumorigenesis - review

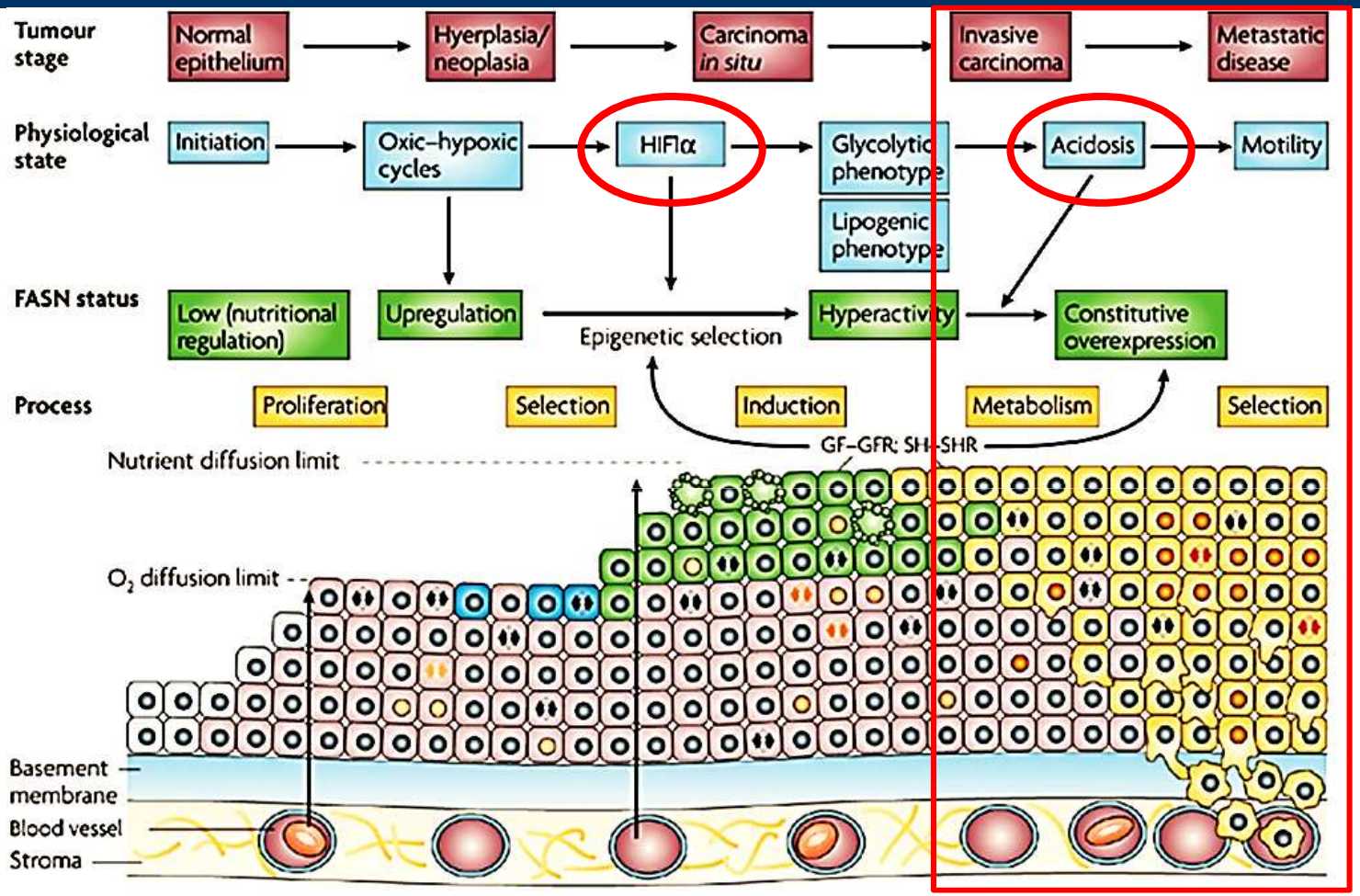




Biochemical abnormalities in tumors 1

- **Respiration**. Glycolysis is a very inefficient way of producing ATP from glucose (2 ATPs in anaerobic conditions) unless all pyruvate end-produced in cytopasm is uptaken by mitochondia and converted to acetyl-CoA as a substrate for citric acid cycle and later to mitochondrial respiration in aerobic conditions. In this way 1 mol of glucose gives 16-times more ATP, 36 mol. Thus, in anaerobic conditions cells have to consume16x more glucose to yield the same amount of ATP than aerobically. Normal eucaryotic cells inhibite unnecessary rate of glycolysis in presence of O_2 **(Pasteur effect; 1857 in yeasts)**. As ATP and citrate cycle products increase in aerobic conditions, the rate of glycolysis drops down, because the ATP and citrate act as allosteric inhibitors for phosphofructokinase 1, the third enzyme in the glycolysis pathway.
- Malignant cells do not show normal Pasteur effect. Instead, **increased glycolysis and lactic acid production continues** even in the presence of adequate oxygen (aerobic glycolysis) **(Warburg effect, 1930).** In addition to Warburg effect, this is due to development of intratumoural regions of hypoxia, arising from disordered vascular development and flow. **Increased glucose uptake** is routinely exploited in **vast majority (> 90%) of human primary and metastatic tumours** through **FDG-PET imaging** (18-fluorodeoxyglucose positron emission tomography). Direct correlation exists between **tumour aggressiveness and the rate of glucose** consumption.
- **Tumor hypoxia.** Hypoxia due to limited diffusion is common even in **premalignant lesions** such as advanced colon polyps. In fact, even early **hyperplasias** contain areas of hypoxia. Once tumour growth carries cells to more than a **few cell layers beyond the basement membrane**, hypoxia due to ineffective O_2 diffusion is envitable. This is evidenced in **benign or malignant tumors** by high expression of **hypoxia-inducible factor 1a (HIF1a)** transcription factor that respond to decreases in available oxygen in cells.
- **Tumor necrosis.** Most of large malignant tumors develop necrosis inside of the mass.

Metabolic changes within tumor promote progression



Most of malignant tumors increase glucose uptake, stimulate glycolysis even in aerobic condition and overproduce lactate **keeping cells in acidotic environment.** Acidosis deepens ischemic hypoxia due to inadequate vasculature to switch on hypoxic genes. Darwinian epigenetic selection turns cells into more robust types and invasive growth to stroma a blood vessel around.

Gatenby, R.A., Gillies, R.J., 2004. Why do cancers have high aerobic glycolysis? Nat. Rev. Cancer 4, 891–899.

Biochemical abnormalities in tumors 2

Enzymes. Intracellular enzyme levels change mainly in anaplastic forms of tumors.

- **Chronic myeloid leukemia (CML)** deficient **alkaline phosphatase** in granulocyte lysosomes due to philadelphia chromosome; **Acute lymphocytic leukemia (ALL)** lymphocytes **lack asparaginase**;
- **Prostatic carcinoma** increase production of **prostatic acid phosphatase (PAP)**;
- **Neuroblastoma** increase production of **neuron-specific enolase**
- 12% of all **malignant tumors** produce **Regan isoenzyme (carcinoplacental alkaline phosphatase (CAP)**, that is produced in normal placenta during pregnancy;
- In many **invasive tumors** lysosomal enzymes (metaloproteases) = **ellastase, collagenase, hyaluronidase** are overexpressed.

Fetal and embryonic proteins. As an example of genetic de-repression and dedifferentiation cancers may express and release proteins **normally present in fetal life** that disappear after birth;**; general phenomenon also present in most experimental cancers inrrespective to carcinogen or physocal dammage.**

- **CEA (carcinoembryonic antigen)** glycoprotein normally present in embryonic GUT cells; reexpressed and released in 75-80% of **colorectal cancer**, but also in 90% **pancreatic Ca, bone Ca, neuroblastoma**, 50-60% **breast Ca**, 75% of **lung Ca**; Small amount (1/40 - 1/10000) Non-tumor reasons: found in normal colon, lung, liver, breast < 5,0 ng/ml; higher in smokers, inflammatory bolwel disease etc.
- **APP (alfa-fetoprotein)** glycoprotein found normally in embryonic liver; small residuum remains after birth; high levels expressed in **germ cell tumors (incl. teratomas**), **hepatocellular carcinoma ; metastasis of other tumors into liver,** Non-tumor reasons: viral hepatitis B, cirrhosis, pregnancy

Tumor-associated hormonal production

Hormone	Tumor	Effect, disorder
Nomotopic overproduction by endocrine tumors		
Gonadotropin	Placental chorfiocarcinoma, hydatiforme mole	
Serotonin	Carcinoid tumors, enterochromatoffin cells	Carcinoid syndrome
Insulin	Insulinoma	Hypoglycemia
Adrenalin	Pheochromocytoma	Hypertension
Cortisol, aldosteron, androgens	Adenoma/ adenocarcinoma of adrenal cortex	Cushing syndrome, Cohn syndrome, Adrenogenital sy.
Ectopic production by non-endocrine tumors		
ACTH or ACTH-like substance	Small cell carcinoma of lungs, Neural tumors, Pancreatic carcinoma	Cushing syndrome
Antidiuretic hormone	Small cell carcinoma of lung	SIADH
Parathyroid hormone (PTH)	Squamous cell carcinoma of lung Breast carcinoma, Renal adenocarcinoma	Hypercalcaemia
Gonadotrophin	Hepatoma, hepatoblastoma Oat cell carcinoma of lungs	Precocious puberty, gynecomastia

Biochemical abnormalities in tumors 3

- **Hormone production.** Endocrine gland can turn into benign adenomas or malignant adenocarcinomas (less common). These tumors overproduce hormones, which gland produces under normal conditions. Certain feedback do not work. Certian non – endocrine tumors can produce hormones as well (ectopic hormonal prod.)
- **Tumour heterogeneity** describes the observation that different tumour cells can show distinct morphological and phenotypic profiles, including cellular morphology, gene expression, metabolism, motility, proliferation, and metastatic potential. Phenomenon occurs both between tumours (**inter-tumour heterogeneity**) and within tumours (**intra-tumour heterogeneity)**. The heterogeneity of cancer cells introduces significant challenges in designing effective treatment strategies. Tumour heterogeneity has been observed in **leukemias, breast, prostate, colon, brain, esophagus, head and neck, bladder and gynecological carcinomas, liposarcoma, and multiple myeloma.**

Two models used to explain the heterogeneity of tumour cells. These are the **cancer stem cell model** and the **clonal evolution model.**

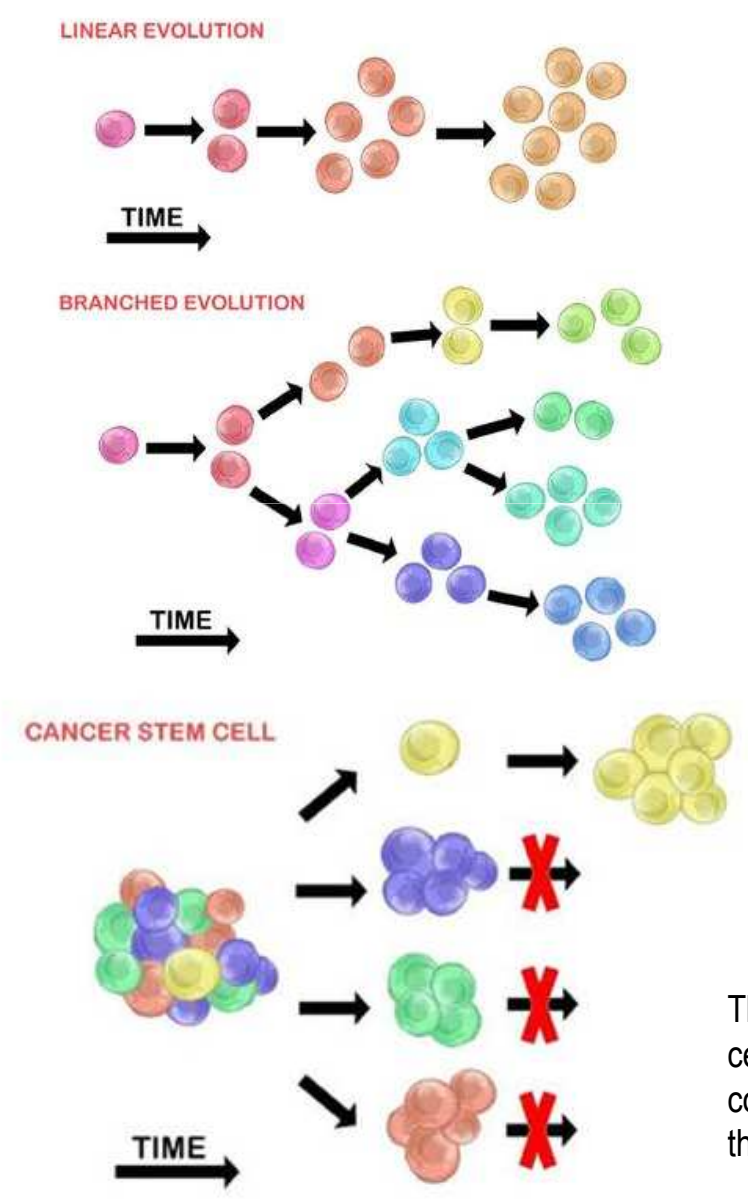
Cancer stem cell model. Tumor is establihed by a small subset of cells within a population of potential tumur cells = **cancer stem cells (CSCs)**. These are marked by the ability to **self-renew and differentiate into non-tumourigenic progeny**. Heterogeneity is the result of differences in the stem cells from which they originated.

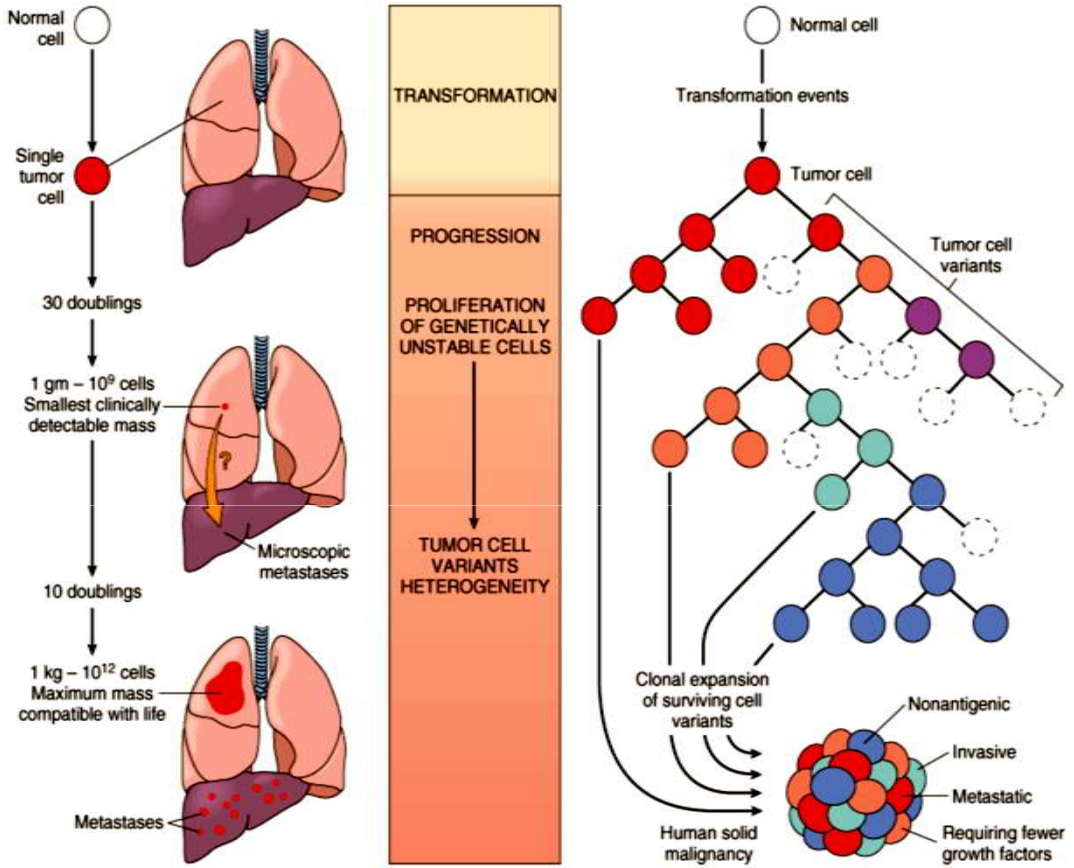
Clonal evolution model 1976 by Peter Nowell **tumours arise from a single mutated cell,** accumulating **additional mutations as it progresses.** These changes give rise to additional subpopulations (**subclones)**, and each of these subpopulations has the ability to divide and mutate further according to evolutionary advantage over the others within the tumour environment.

Linear expansion = sequential mutations accumulate in tumour suppressor genes, and DNA repair genes resulting in clonal expansion of tumour cells.

Branched expansion = multiple subclonal populations occurs through a splitting mechanism; acquisition of mutations is random as a result of increased genomic instability with each successive generation.

Tumor heterogenity – stem cell and clonal concepts





The long-term mutational accumulation may provide a selective advantage during certain stages of tumour progression. The tumour microenvironment may also contribute to tumour expansion, as it is capable of altering the selective pressures that the tumour cells are exposed to.

Terminology

Tissue of Origin	Benign	Malignant
Connective tissue and derivatives	Fibroma Lipoma Chondroma Osteoma	Fibrosarcoma Liposarcoma Chondrosarcoma Osteogenic sarcoma
Endothelial and related tissues	Hemangioma Lymphangioma	Angiosarcoma Lymphangiosarcoma Synovial sarcoma, Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cells		Leukemias, Lymphomas
Muscles	Leiomyoma Rhabdomyoma	Leiomyosarcoma Rhabdomyosarcoma
Tumors of epithelial origin	Squamous cell papilloma Adenoma Papilloma Cystadenoma Bronchial adenoma Renal tubular adenoma Liver cell adenoma Transitional cell papilloma Hydatidiform mole	Squamous cell carcinoma Adenocarcinoma Papillary carcinomas Cystadenocarcinoma Bronchogenic carcinoma Renal cell carcinoma Hepatocellular carcinoma Transitional cell carcinoma Choriocarcinoma

Special forms of tumors

- **Teratoma** - benign tumors arising from germ cells; contain derivatives of different germ layers (skin, neurons, glial cells, thyroid, intestinal epithelium, and cartilage) occur principally in the gonads, mediastinum
- **Hamartoma** – tumor-like non-neoplastic mass containing mess of normal tissue (cartilage, ducts or bronchi, connective tissue, blood vessels, and lymphoid tissue); arising due to altered differentiation in embryogenesis
- **Choristoma** – small ectopic islands of normal tissue (e.g pancreatic tissue in the wall of the stomach or intestine, adrenal rests under the renal capsule, and nodules of splenic tissue in the peritoneal cavity.
- **Polyps -** benign tumors; represent overgrowth of normal tissue (e.g vocal cord polyps, skin tags, and hyperplastic polyps of the colon).

Secondary description

- papillary - describes a frondlike structure
- medullary - signifies a soft, cellular tumor with little connective tissue stroma,
- scirrhous or desmoplastic - implies a dense fibrous stroma
- colloid carcinomas - secrete abundant mucus, in which float islands of tumor cells
- comedocarcinoma is an intraductal neoplasm in which necrotic material can be expressed from the ducts

Etiology of cancer

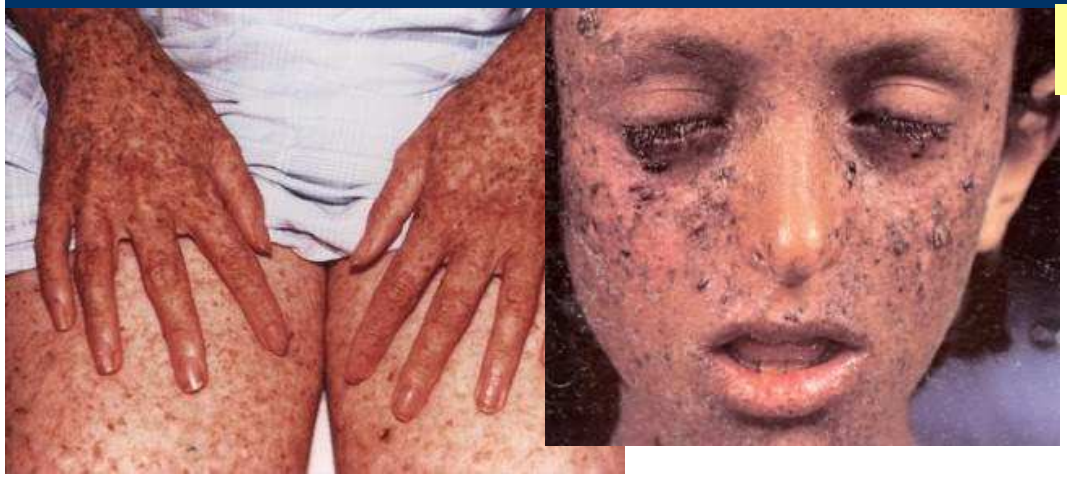
- Genetic factors
- Carcinogens – chemical factors
- Physical factors
- Oncoviruses

1. Hereditary predisposition to cancer

1. Inherited Cancer Syndromes (Autosomal Dominant)	
Gene	***Inherited Predisposition***
RB	Retinoblastoma
p53	Li-Fraumeni syndrome (various tumors)
p16INK4A	Melanoma
APC	Familial adenomatous polyposis/colon cancer
NF1, NF2	Neurofibromatosis 1 and 2
BRCA1, BRCA2	Breast and ovarian tumors
MEN1, RET	Multiple endocrine neoplasia 1 and 2
MSH2, MLH1, MSH6	Hereditary nonpolyposis colon cancer
PATCH	Nevoid basal cell carcinoma syndrome
2. Familial clustering of cancer cases (Familial Cancers)	
Variable	Breast cancer, Ovarian cancer, Pancreatic cancer
3. Inherited Syndromes of Defective DNA Repair (Autosomal Recessive)	
Many	Xeroderma pigmentosum, Ataxia-telangiectasia Bloom syndrome, Fanconi anemia

Genetic and environmental factors contribute to the development of cancer, environmental muatational effects appear to be the dominant risk factors for most cancers.

Diseases with tumors and inborn DNA-repair defects



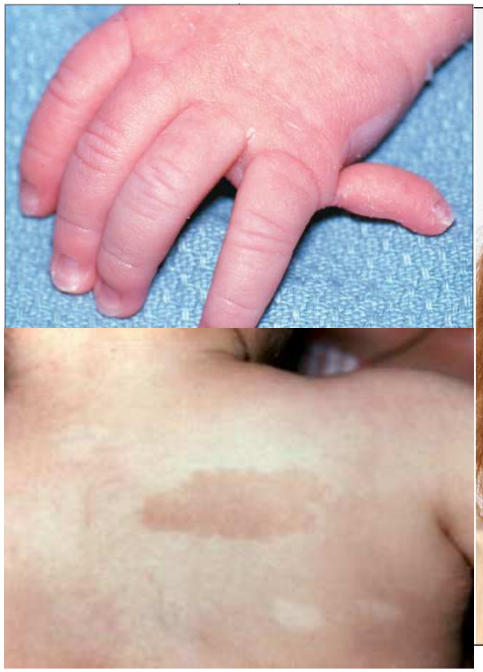
Xeroderma pigmentosum

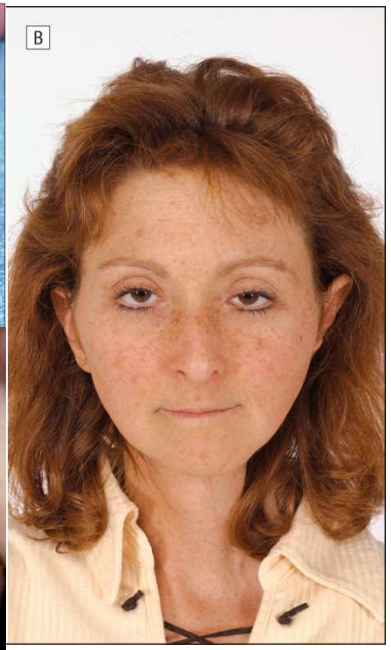
rare autosomal recessive genetic defect in nucleotide excision repair (NER) system 1: 250,000, Japanese damage caused by ultraviolet (UV) light

basal cell carcinomas (basaliomas) and other skin malignancies metastatic malignant melanoma and squamous cell carcinoma

Fanconi anemia

- rare AR-linked genetic disease. 90% develop bone marrow failure ; **there is 17 genes resposnible for FA** involved in the recognition and repair of damaged DNA: FANCA, FANCB, FANCC, etc.including BRCA1; frequency in Ashkenazi Jews is 1/90
- short stature, strabism, deafdness, low set ears, pale skin, pigmentation (café au lait spots), abnormal or missing thumb, feeling tired, infections; by age of 40, 98% of FA patients will have develop hematological abnormality: trombocytopenia (petechiae, bruises), megaloblastic anemia, pancytopenia, Tumors: **myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)**.





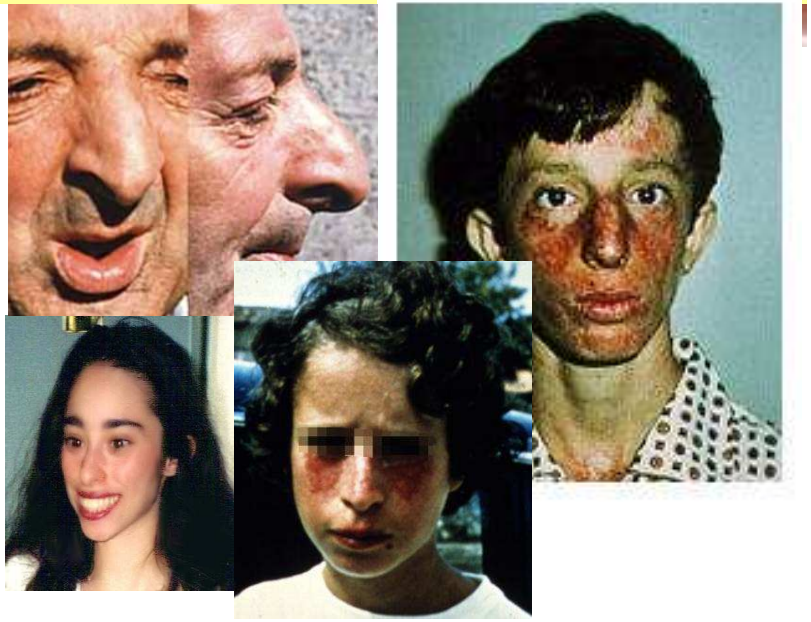
Diseases with tumors and inborn DNA-repair defects

- complex autosomal recessive synd. with neurological (**ataxia due to cereberal damage**), immunological (**deficient maturation of T-Ly**), liver, skin, and endocrine abnormalities **Telangiectasia** (dilated blood vessels) over the white (sclera) of the eyes
- **defective gene ATM,** 11q22-q23. encodes **DNA-dependent proteinkinase** (ATM), involved in cell cycle regulation with p53 protein. ATM proteikinase is activated after double strand DNA breaks to initiate repair mechanisms. Disabling mutation of ATM is limiting DNA- repair mech. and lead to increased sensitivity to UV radiation and tendency to malignancy: **lymphomas and leukemia**,
- treatment to avoid the use of radiotherapy and radiochemotherapy

- **Bloom syndrome** (BS) rare AR-disorder characterized by short stature, predisposition to cancer and genomic instability**. defective gene BLM 15q26.1** encodes **DNA helicase** suppress inappropriate homologous recombination
- BLM gene leading to **mutated DNA helicase** protein formation. genomic instability that includes excessive crossovers between homologous chromosomes and sister chromatid (SCEs).
- skin **erythematous rash in cheeks, nose** , **telangiectatic,** infiltrated, head disproportionaly small, micrognatia, chronic obstruct. broncho-pulm. disease., immune deficiency, Hypogonadism, diabetes, **leukemias, lymphomas, carcinomas**

Ataxia telangiectasia (sy. Louis Barr)

Bloom syndrome



2. Carcinogens – chemicals promoting cancer

1. Direct-Acting Carcinogens

- **Alkylating Agents**
  - ß-Propiolactone
  - Dimethyl sulfate
  - Diepoxybutane
  - Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
- **Acylating Agents**
  - 1-Acetyl-imidazole
  - Dimethylcarbamyl chloride

2. 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 (ß-naphthylamine)
  - Benzidine
  - 2-Acetylaminofluorene
  - Dimethylaminoazobenzene (butter yellow)
- **Natural Plant and Microbial Products**
  - Aflatoxin B
  - Griseofulvin
  - Cycasin
  - Safrole
  - Betel nuts
- **Others**
  - Nitrosamine and amides
  - Vinyl chloride, nickel, chromium
  - Insecticides, fungicides
  - Polychlorinated biphenyls

Carcinogens (cont')

- **Direct-Acting Alkylating Agents** - activation independent weak
  - **anticancer drugs** (e.g., cyclophosphamide, chlorambucil, busulfan, and melphalan) - lymphoid neoplasms, leukemia, etc. (interacting, damaging DNA)
  - **immunosuppressive drugs** - cyclophosphamide (rheumatoid arthritis and Wegener granulomatosis).
- **Polycyclic Aromatic Hydrocarbons** - require metabolic activation, most potent
  - tumors in a wide variety of tissues and species (skin - skin cancers; subcutaneously - sarcomas;
  - polycyclic hydrocarbons (combustion of tobacco, particularly with cigarette smoking - lung and bladder cancers),
  - animal fats – smoked, fied meats and fish
- **Aromatic Amines and Azo Dyes**
  - carcinogenic in liver; "ultimate carcinogen" is formed by cytochrome P-450 oxygenase
  - acetylaminofluorene (hepatocellular carcinomas)
  - ß-naphthylamine (bladder cancer) - aniline dye and rubber industries; excreted in the urine, split by the urinary glucuronidase (humans)
  - azo dyes - food coloring (e.g., butter yellow, scarlet red).
- **Naturally Occurring Carcinogens.**
  - mycotoxin aflatoxin B1 (Aspergillus flavus) - improperly stored corn, rice, and peanuts (hepatocellular carcinoma in Africa and China)

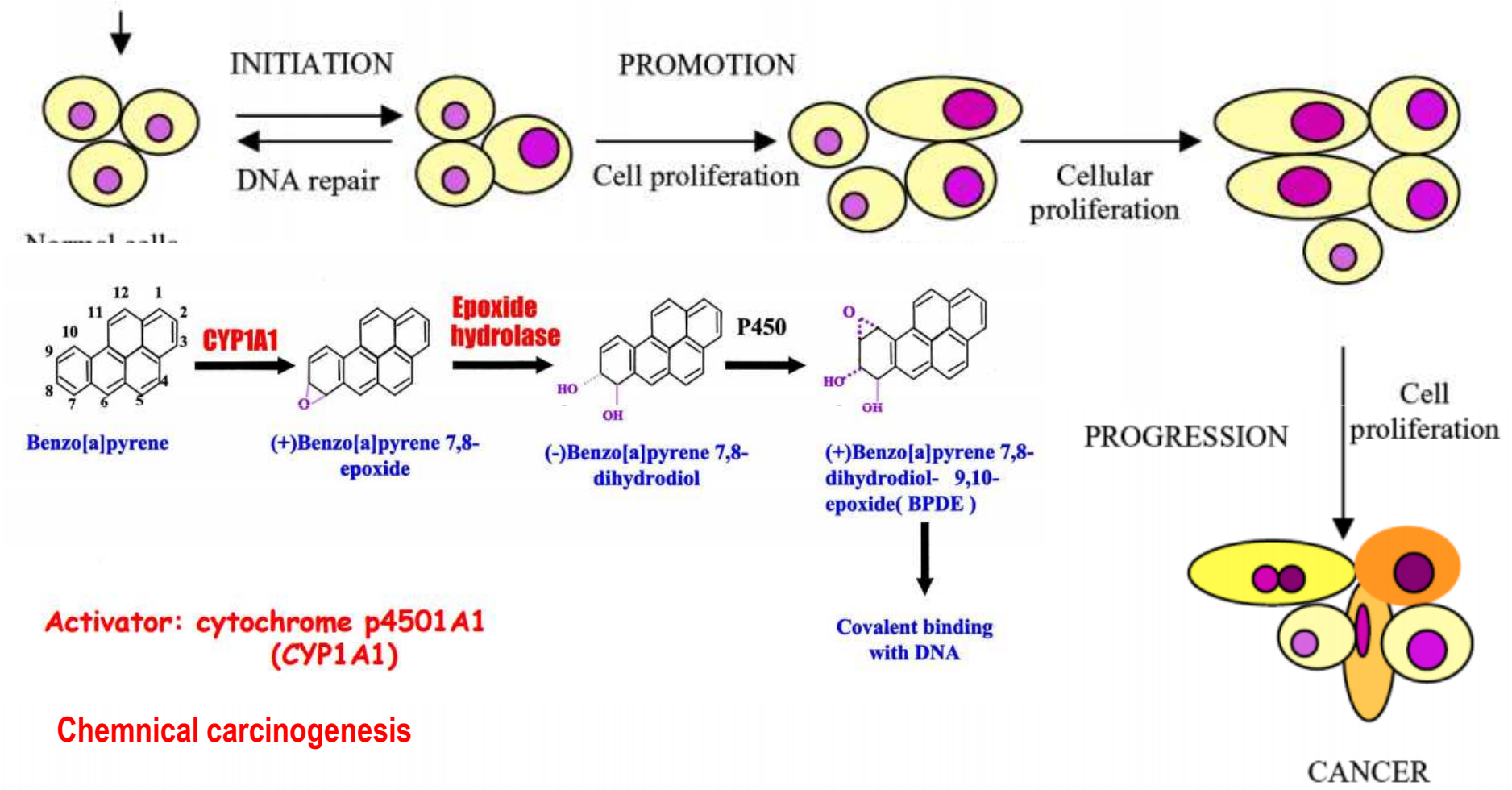
Carcinogens (cont')

- **Nitrosamines and Amides (nitrate preservatives)**
  - formed in the gastrointestinal tract of humans (induction of gastric carcinoma); derived in the stomach from the reaction of nitrostable amines and nitrate used as a preservative, which is converted to nitrites by bacteriia

- **Miscellaneous Agents**
  - asbestos - bronchogenic carcinomas, mesotheliomas, and gastrointestinal cancers
  - vinyl chloride (monomer of polyvinyl chloride) - hemangiosarcoma of the liver
  - Chromium, nickel, and other metals -cancer of the lung when volatilized and inhaled .
  - arsenic - skin cancer associated
  - insecticides (aldrin, dieldrin, and chlordane and the polychlorinated biphenyls) - carcinogenic in animals

- **Promoters of Chemical Carcinogenesis**.
  - exogenous agents, such as cigarette smoke or viral infections - tissue damage and reactive hyperplasia.
  - endogenous promoters - bile salts (dietary fat - colon cancer), hormones (estrogens - liver tumors; diethylstilbestrol - postmenopausal endometrial carcinoma; alcohol (cancers of the mouth, pharynx, larynx by more 10x

Multistage chemical carcinogenesis

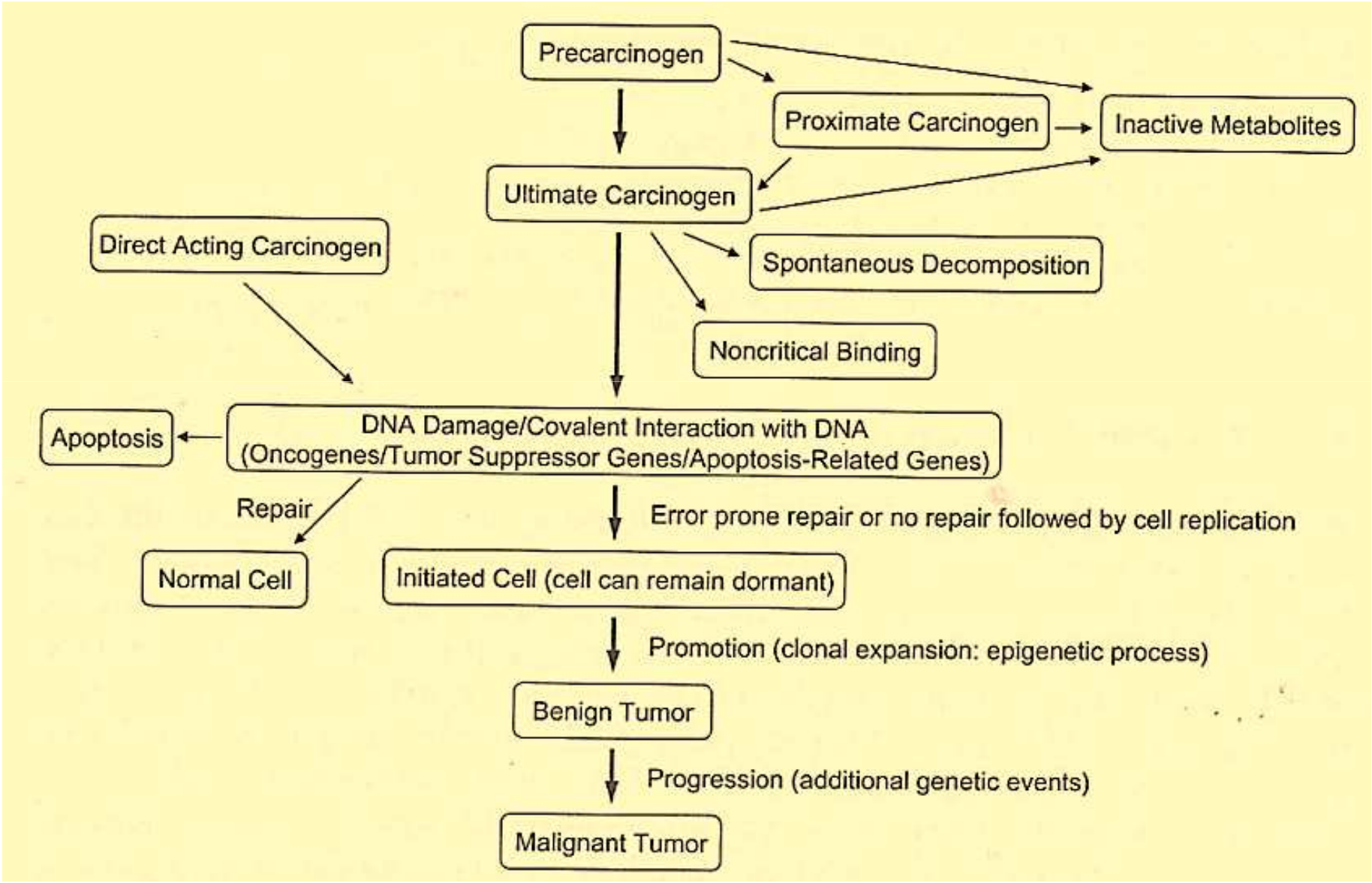


Chemnical carcinogenesis

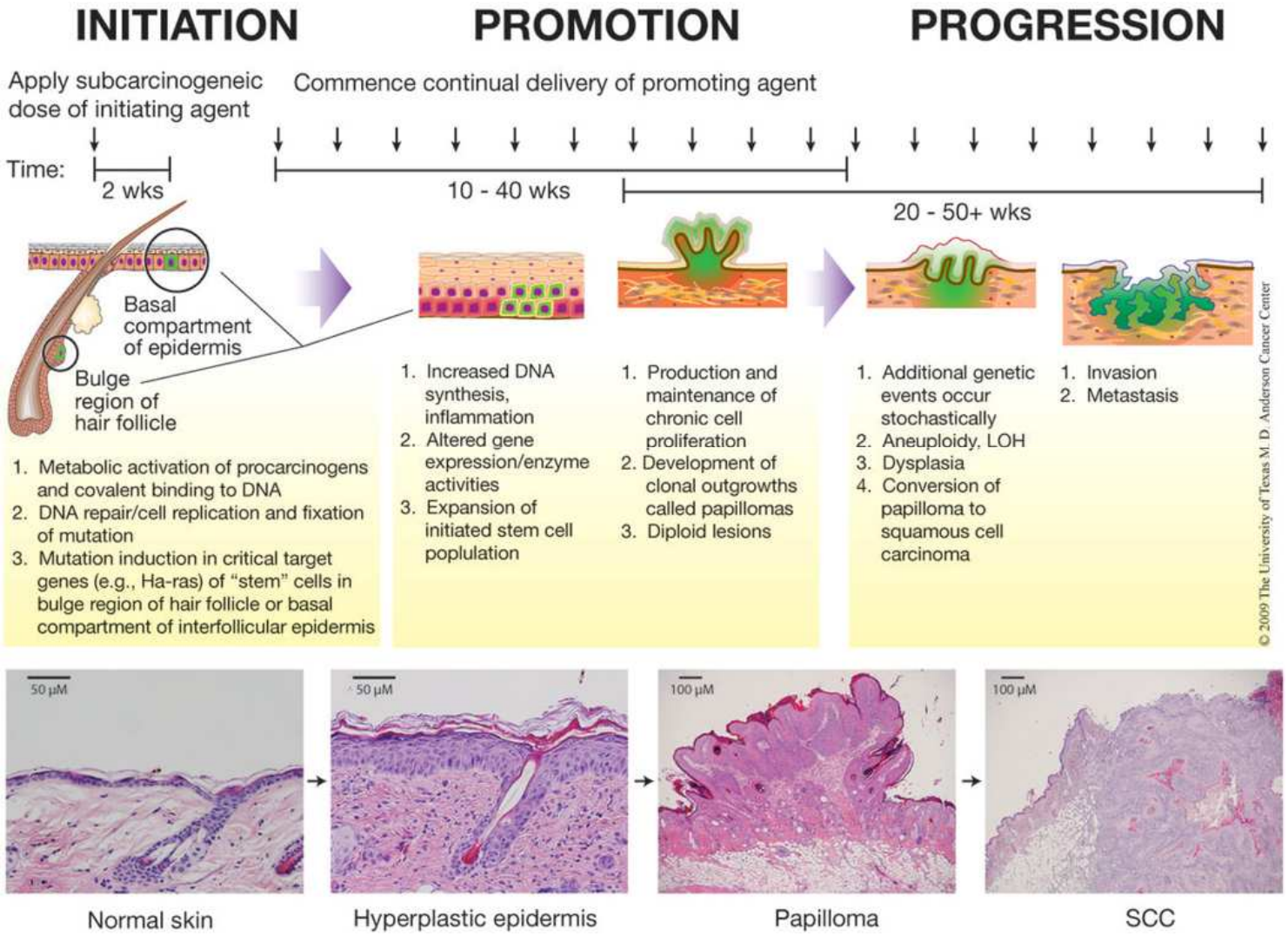
Genotoxic: carcinogens that interact with DNA resulting in mutation

Nongenotoxic: carcinogens that modify gene expression but do not damage DNA

Steps in chemical carcinogenesis



Two-stage model of skin carcinogenesis in mice



In two-stage skin carcinogenesis experiments, initiation occurs following a single subcarcinogenic dose of a carcinogen such as 7,12-dimethylbenz[a]-anthracene (DMBA) This event is irreversible; however, no visible tumors will appear until 'promoted' by the repeated application of a tumor promoting agent such as the phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA)

Initiators and promotors

Initiating agents	Genetic Target[a]	**Promoting agents**	Initial molecular target or event associated with tumor promotion
DMBA	*Hras1, Kras*	TPA	Protein Kinase C
Benzo[a]pyrene (B[a]P)	*Hras1*	Telocidin	Protein Kinase C
MNNG	*Hras1, Kras*	Okadaic acid	Protein Phosphatases -1 and -2A
N-methyl-*N*-nitrosourea (MNU)	*Hras1*	Chrysarobin	Generates oxidative stress
Bis(chloromethyl)ether	Unknown	Benzoyl peroxide	Generates oxidative stress
Ultraviolet radiation	*Tp53, Nras*	Ultraviolet radiation	Protein Kinase C, EGFR
Cisplatinum	*Hras1*	Wounding	Stimluation of EGF receptor
β-propiolactone	*Hras1*		

Examples of chemical or physical agents that can serve as initiating or promoting agents and their primary molecular target or event

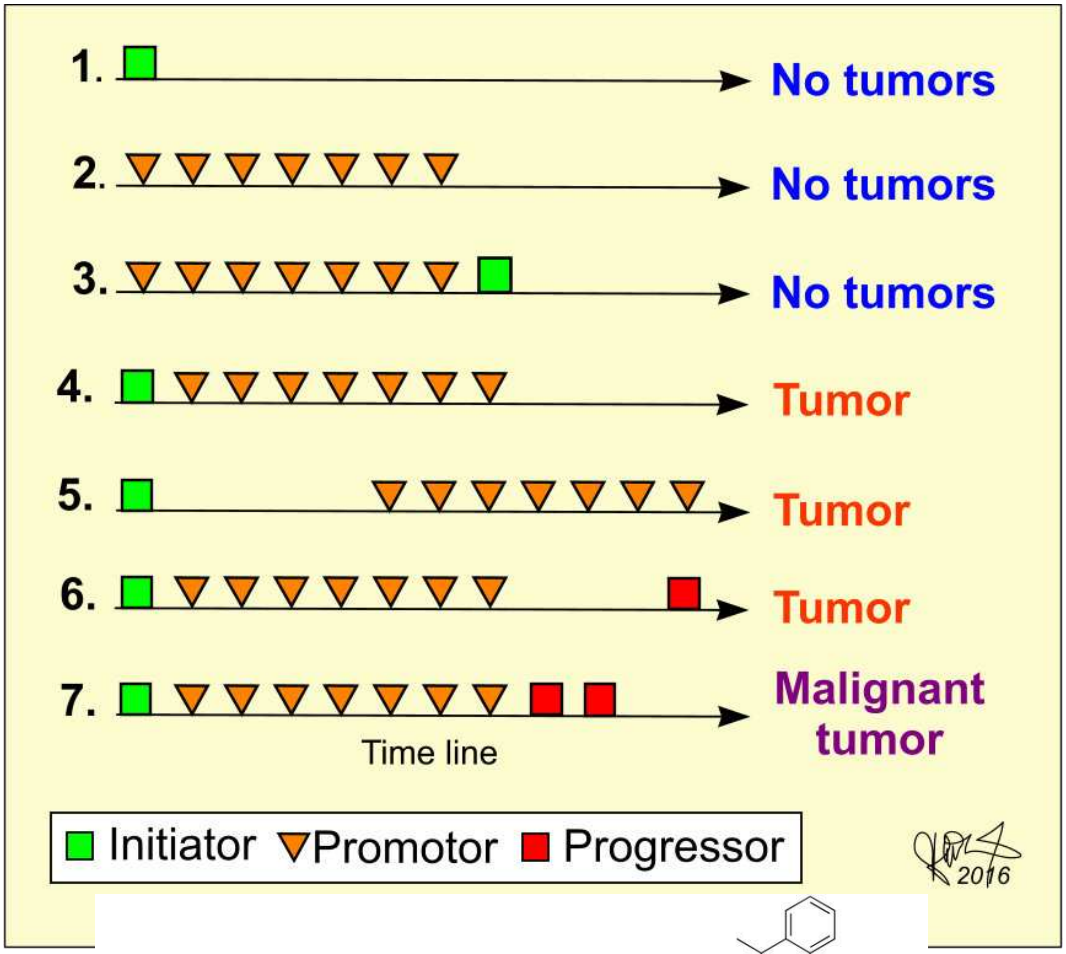
Multistage chemical carcinogenesis

To produce a tumor, carcinogens are to be applied in precise order and repetition, at approriate timing.

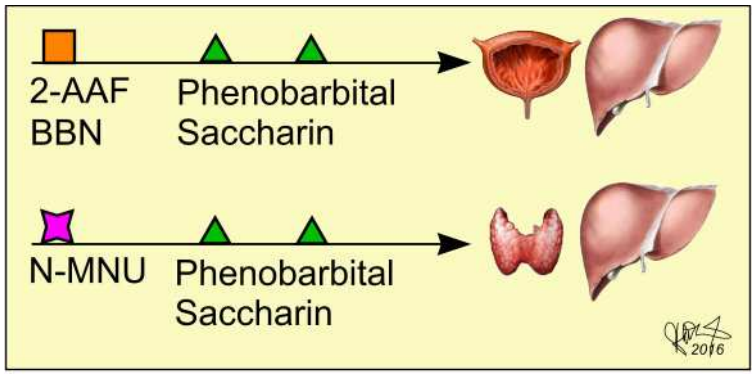
1. Initiation (genotoxic) Only certain chemicals are suitable for tumor induction via direct genetic damage (mutations).

2. Promotion (non-genotoxic) Involves a selecti-ve clonal expansion of initiated cells by additional genetic or non-genetic alterations leading to benign tumors/ pre-malignant lesions.

3. Progression (genotoxic) Additional DNA damage (chromosomal aberrations, translocation) tstart malignancy.

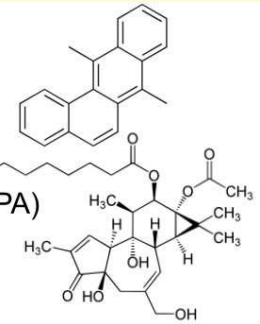


Coupling different chemical lead to different tumors



N-methylnitrosourea (N-MNU)
2-Acetylaminofluorene (AAF, 2-AAF)
N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN)

7,12-Dimethylbenz[a]anthracene (DMBA)



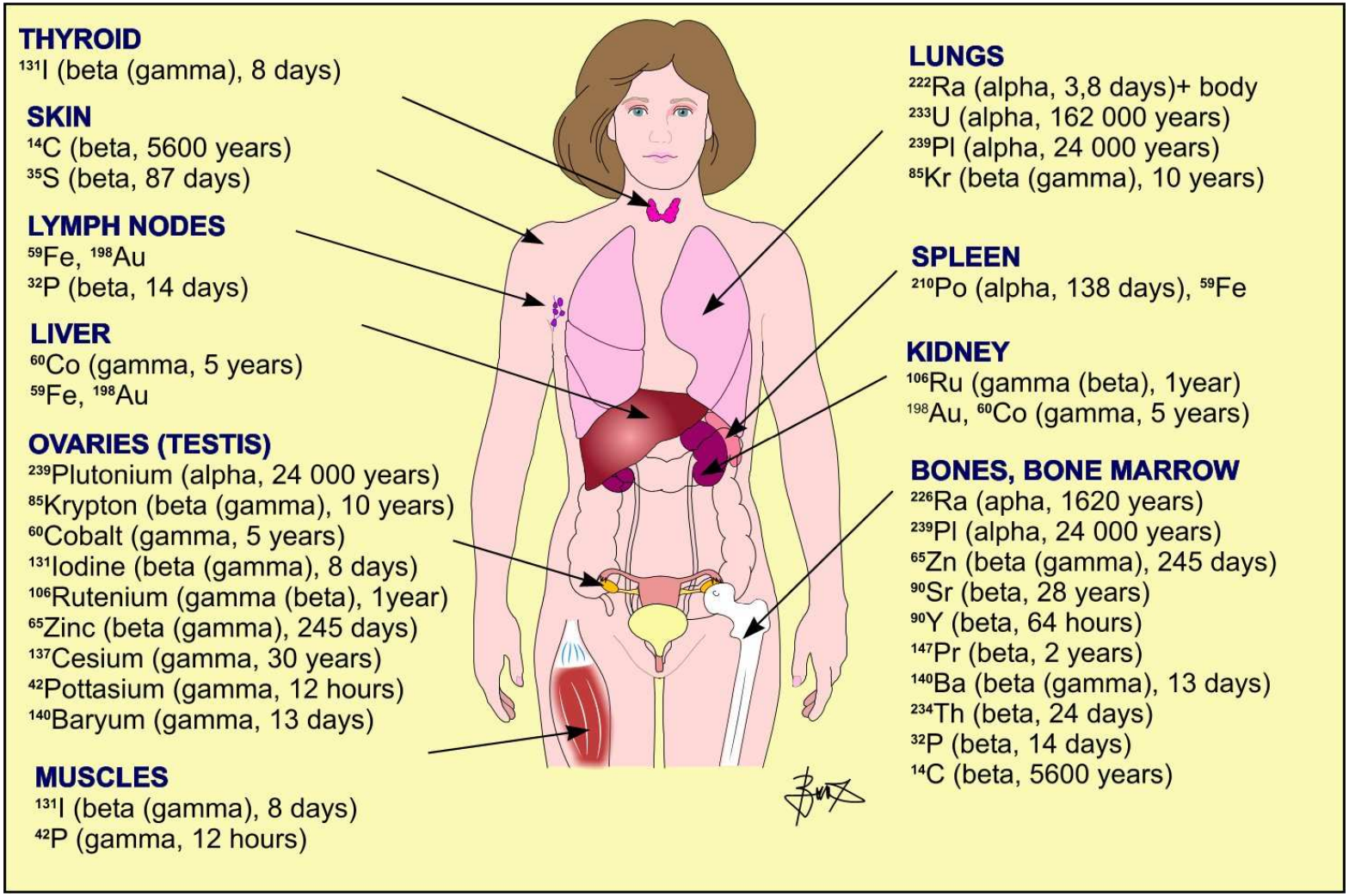
12-O-tetradecanoylphorbol-13-acetate (TPA)

3. Physical carcinogenic factors

- **Ultraviolet radiation**
  - Type of cancer: Tumours: squamose cell carconoma, malignant melanoma
  - Cases: increased rate of tumours in people with white skin and close to equator (Queensland, Australia)
  - damage depends on the type and intensity of UV – radiation: UVA (320 to 400 nm), **UVB** (280 to 320 nm), and UVC (200 to 280 nm; absorbed in ozone layer) and melanin content
  - Effects: inhibition of cell division, inactivation of enzymes, DNA mutations (pyrimidine dimers in DNA), necrosis; mechanism of damage: exhaustion of NER (nucleotide excision repair)
  - increased rate of DNA damage w/o repair - **xeroderma pigmentosum** (AR) – extreme photosenzitivity, 2000-x higher risk of tumors after sunbathing
  - UVB - mutant forms of RAS and p53 gens in animals and man

- **Ionizing radiation** (practically any tumor), synergic effect together with carcinogens
  - Hiroshima a Nagasaki – acute & chronic myeloid leukemia; later solid tumors (e.g., mammary Ca, Ca of colon, Ca of thyroid gland, bronchogenic carcinoma
  - Marshall islands - 90% of the children under age 10 years on Rongelap Island developed thyroid nodules within 15 years, and about 5% of these nodules proved to be thyroid Ca
  - Tchernobyl - 2000 cases of thyroid cancers have been recorded in children living in the area.
  - Types of cancer: **Thyroidal cancer** – kids; 9% of kids with s X- ray scans of the neck and face done 2x per year; **Leucaemia** – 10 to 12-fold rise after therapeutical irradiation (CLL never occurs after irradiation); **Mammary carcinoma, lung cancer, salivary gland cancers** (GIT cancer is rare)

Deposition of radioactive isotopes in the body



Radiosensitive organs - lymphatic tissue, intestine mucosa, bone marrow, gonads
Radioresponsive organs - connective tissue, bones, epithelium, endothelium
Radioresistent organs - brain, muscles, liver, endocrine glands

4. Oncogenic viruses

Virus	Species	Tumor
1. DNA viruses		
Polyomaviridae		
Papilloma virus	Man, rabbit, cattle	**Papillomas**
Polyoma virus, SV40	Rodents	Various solid tumours, sarcoma
Adenoviridae		
Adenovirus type 9,12, 18, 31	Rodents	Various solid tumours
Herpesviridae		
Marek' virus	Chicken	Lymphomatosis
Lucke virus	Frog	Adenocarcinoma
Epstein-Barr' virus	Man	**Burkitt' lymphoma, Nasofaryngeal Ca, B-cell lymphoma, Hodgkin lymphoma**
Herpes simplex typ 2	Man	**Ca cervicis uteri**
Herpesvirus saimiri	Monkey	Lymphoma
KSHV (HHV-8)	Man	**Kaposi sarcoma, Primary effusion lymphoma**
Poxviruses		
Shope fibroma virus	Rabbit	Fibroma
Yaba monkey virus	Monkey	Papilloma
Hepadnavirus		
HBV (hepatitis B virus)	Man	**Hepatoceullar carcinoma**

Oncogenic viruses (cont.)

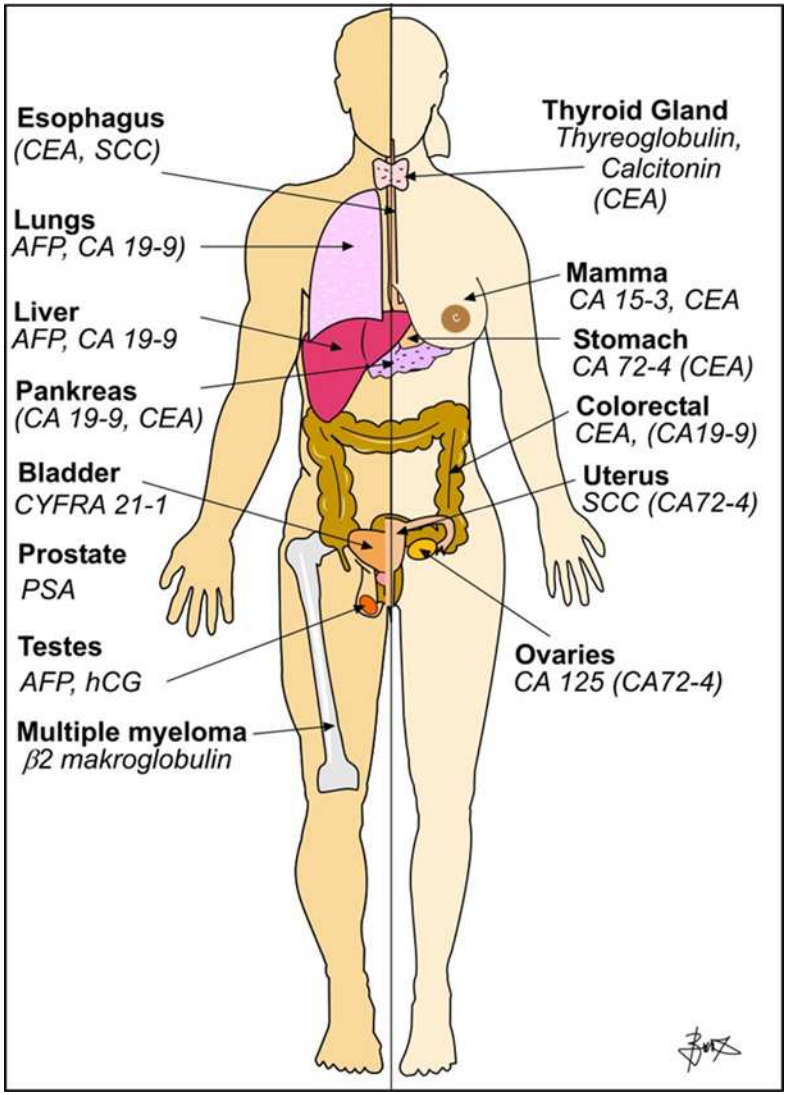
Virus	Species	Tumour
2. RNA viruses		
Sarcoma viruses		
Rous' sarcoma virus	Chicken	Sarcoma
Murine sarcoma viras	Mouse, Rat	sarcoma
Feline sarcoma virus	Cat, dog, rabbit	Sarcoma
Bovine lymfosarcoma virus	Cattle	Sarcoma
Leukaemic viruses		
Avian leukaemia virus	Birds	Adenocarcinoma
Murine leukaemic virus (Gross-Rauscher-Friend)	Mouse, rat	Leukaemia
Bovinne leukaemia virus	Cattle	Leukaemia
Feline leukaemia virus	Cat, dog, rabbit	Leukaemia
Herpesvirus saimiri	Monkeys	Lymphoma
Mammary carcinoma viruses		
Mouse mammary carcinoma virus (Bittner-Muhlbock)	Mouse	Breast cancer

Clinical considerations Diagnostics

Diagnostics of cancer

- **Clinical evaluation -** invaluable for optimal pathologic diagnosis, often underestimated
  - Symptomatology – from primary leasion or metastases (endocrine – paraneopastic, pain, bleeding)
  - Imaging techniques - USG, CT, NMR – evidence of primary tumor, metastasis
  - Probatory surgery – spreading of tumours

  Radiation changes in the skin or mucosa can be similar to those in cancer. Sections taken from a healing fracture can mimic anosteosarcoma
- **Laboratory diagnostics**
  - **Histology and cytology** (imunohistochemistry)
  - **Biochemical methods**



Tumour markers in diagnostics of various types of cancers

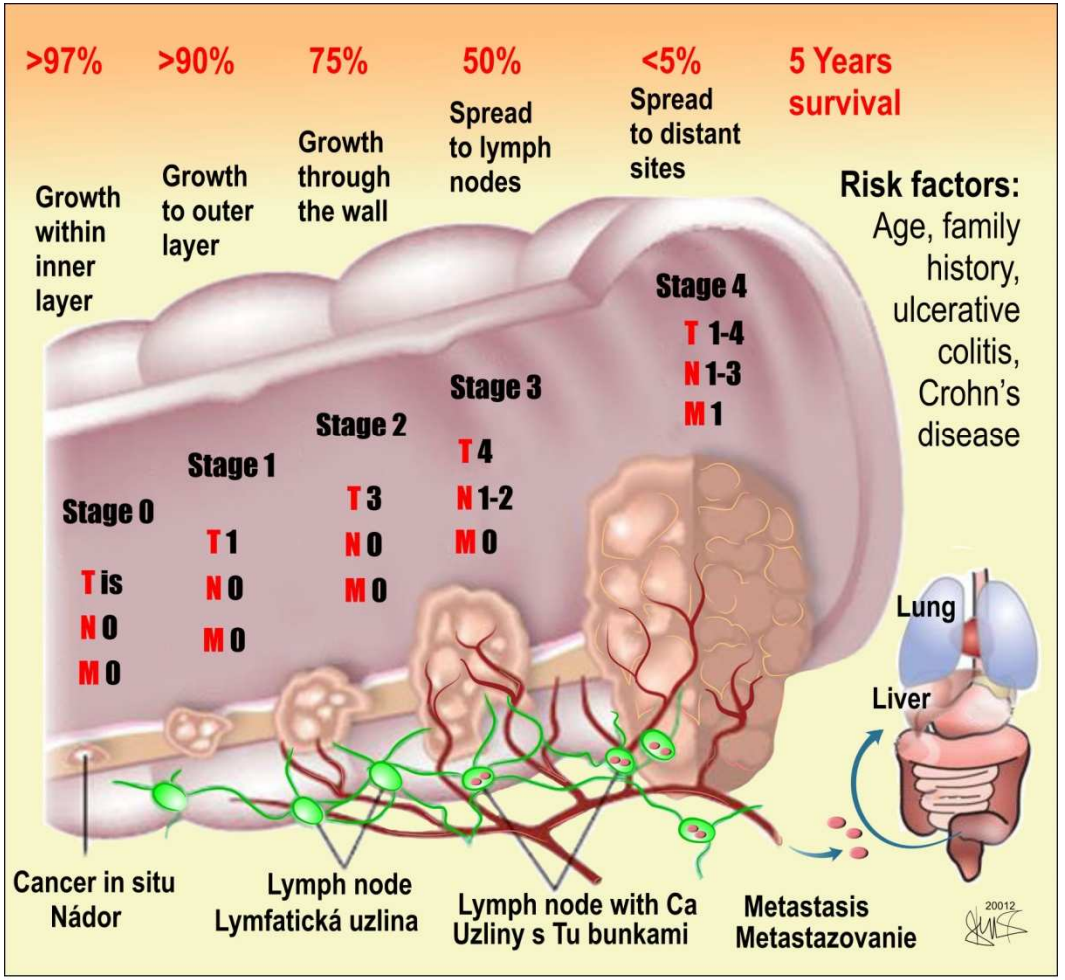
Staging and grading

A. Grading of a cancer

- degree of differentiation of Tu cells + the number of mitoses within Tu → neoplasm's aggressiveness
- **grades I to IV** - histologic quantification of changes betw anaplasia and normal cells

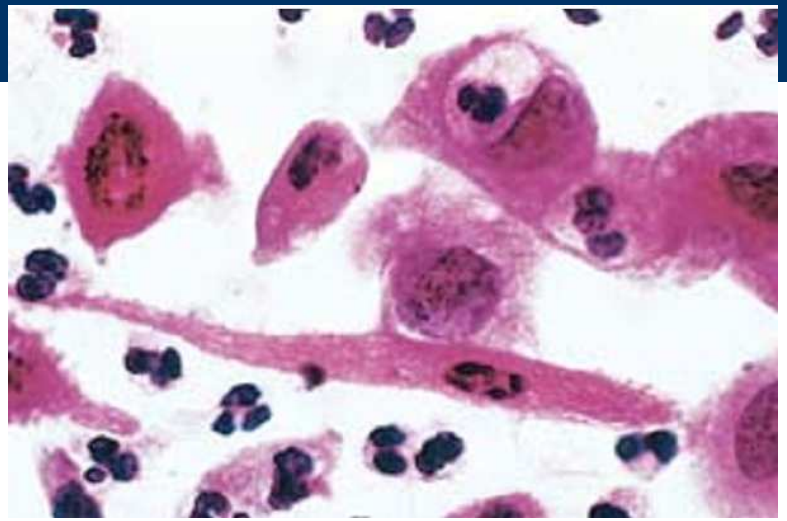
B. Staging of cancer

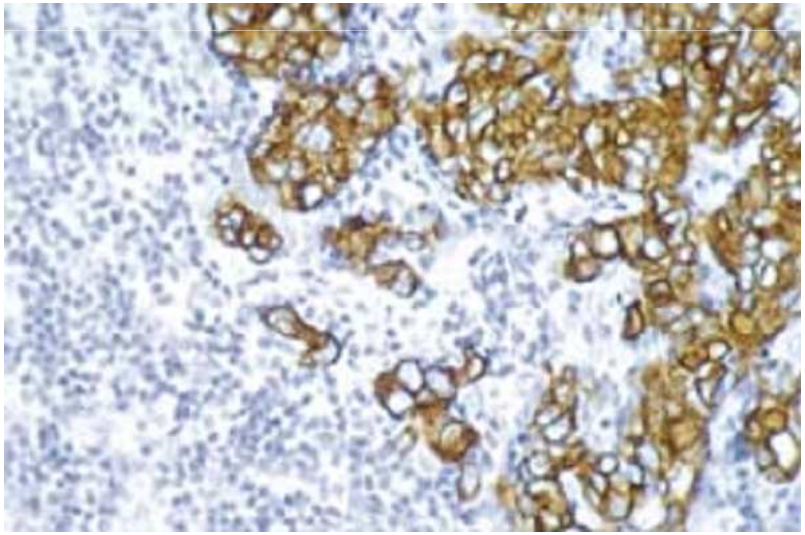
- size of the primary lesion + extent of spread to regional lymph nodes + the presence/ absence of blood-borne metastases
- Union Internationale Contre Cancer (UICC) - **TNM system**
  - T for primary tumor (T0 - in situ lesion; T1 - T4; outgroet through borders),
  - N : regional lymph node involvement (N0 - no, N1 to N3 increasing number and range)
  - M : metastases (M0 no distant mets, M1 – M2 the presence of blood-borne mets and some judgment as to their number (M2)
- American Joint Committee (AJC) on Cancer Staging - **stages 0 to IV**
  - within each of these stages the size of the primary lesions and the presence of nodal spread and distant metastases is evaluated



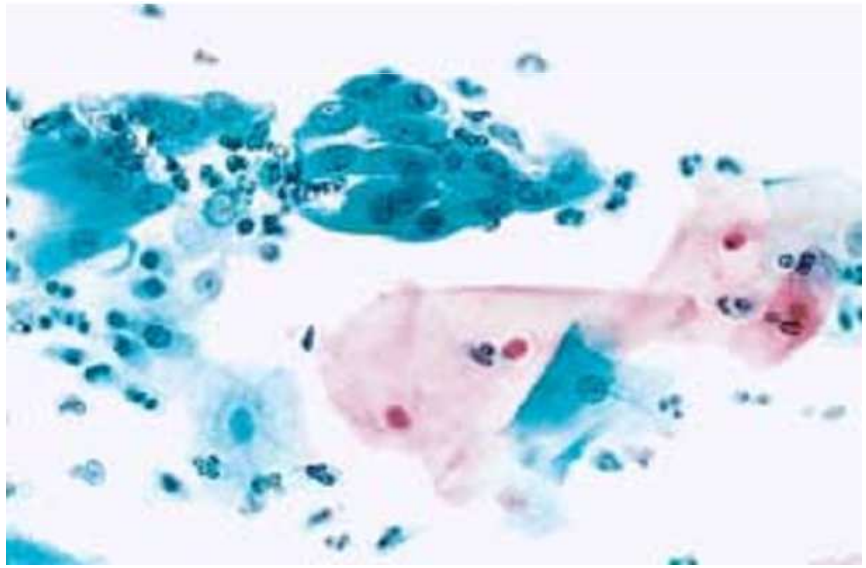
Histology and cytology

- **Excision or biopsy** – per-surgery "quick-frozen section" (in large tumors margins may not be representative and the center may be largely necrotic)
- **Fine-needle aspiration** –palpable lesions (breast, thyroid, lymph nodes)
- **Cytologic (Pap) smears** – cervix uteri,





Anticytokeratin immunoperoxidase stain of a tumor of epithelial origin (carcinoma).



Abnormal cervicovaginal smear - numerous malignant cells that have pleomorphic, hyperchromatic nuclei

Tumor markers

Markers	Associated Cancers
1.Hormons	
Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors, Ectopic hormones
2. Oncofetal Antigens elevated in serum	
Alfa-Fetoprotein (AFP) *AFP gene (4q25)*	major plasma protein produced by yolk sac & liver in fetus; stops by 8m after birth Hepatocellular carcinoma; Nonseminomatous germ cell tumors of testis; neuroblastoma, hepatoblastoma,
Carcinoembryonic antigen (CEA) CEA family 29 members *CEACAM genes 1 - 26*	produced in gastrointestinal tissue in fetus ; stops before birth colorectal carcinoma (represents L and E -selectins) pancreas, lung, stomach, and heart, cervix cancer, ovarian cancer, breast cancer, urinary tract cancer, postive in heavy smokers, ulcerative colitis, pancreatitis, cirrhosis, COPD, Crohn's disease, hypothyroidism
3. Isoenzymes	
Prostatic acid phosphatase (AP)	Prostate cancer
Neuron-specific enolase (NSE)	Small cell cancer of lung, neuroblastoma
4. Specific Proteins	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen,	Prostate cancer

Tumor markers

Markers	Associated Cancers
5. Mucins and Other Glycoproteins (CA – Cancer Antigen) elevated in serum	
CA-125 (Mucin 16) Gene: MUC 16	Ovarian cancer, pancreas, uterus
CA-15-3 / CA 27.29 (Mucin 1) Gene: MUC1 (different epitopes on the same protein antigen); CA27.29 has enhanced sensitivity and specificity)	Breast cancer: 30% low-stage disease ; 60 -70% advanced-stage CA15-3/CA27.29: benign ovarian cysts, benign breast disease, and benign liver disease; cirrhosis, sarcoidosis, lupus. CA27.29 : non-breast malignancies including colon, stomach, pancreas, prostate and lung.
CA-19-9 Sialyl-Lewis Antigen an antibody that binds to the tumor surface marker Sialyl-Lewis A)	Pancreatic cancer (!! false negative{ positive in many cases) Colorectal cancer, esophageal cancer, hepatocellular carcinoma. Pancreatitis, cirrhosis, diseases of the bile ducts (obstructive icterus)
CA-50 / CA 242 non-fucosylated Sialyl-Lewis precursors ; sialyllacto-N-tetraose	Tumor of head, colon, pancreas, mammary gland non-sialylated Lewis antige (CA 195, CAM43 , CA494)
CA-72-4 onkofetální nádorové marker.	Stomach cancer Eosphagus, colon, pancreas, ovarial Ca Liver cirrhosis, pancreatitis, inflammatory bowel disase
6. Mutated gene products/ Tissue based markers	
p53, APC, RAS *p53 and RAS* *p53*	Colon cancer (stool and serum) Pancreatic cancer (stool and serum) Lung cancer (sputum and serum) Bladder cancer (urine)

Paraneoplastic syndromes

Clinical Syndromes	Major Forms of Cancer	Causal Mechanism
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone (SIADH)	Small cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma, Renal adenocarcinoma Adult T-cell leukemia/lymphoma Ovarian carcinoma	Parathyroid hormone-related protein (PTHRP), TGF-a, TNF, IL-1
Hypoglycaemia	Fibrosarcoma Mesenchymal sarcomas Hepatocellular carcinoma	Insulin or insulin-like substance
Carcinoid syndrome	Bronchial adenoma (carcinoid) Pancreatic carcinoma Gastric carcinoma	Serotonin, bradykinin
Polycythemia	Renal carcinoma Cerebellar hemangiom Hepatocellular carcinoma	Erythropoietin

Paraneoplastic syndromes (cont'd)

Clinical Syndromes	Major Forms of Cancer	Causal Mechanism
CNS, PNS and Muscle Syndromes		
Myasthenia	Bronchogenic carcinoma	Immunologic cross reaction
Neuropathies, cortical cerebellar deg., polymyositis - like	Breast carcinoma, others	*Neural antigens ectopically expressed by visceral cancers*
Dermatologic Disorders Osseous, Articular, and Soft Tissue Changes		
Acanthosis nigricans	Gastric, Lung, Uterine Ca	Immunologic; epidermal growth factor
Dermatomyositis	Bronchogenic, breast carcinoma	Immunologic
Hypertrophic osteoarthropathy	Bronchogenic carcinoma (10%)	*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	*Thymic neoplasms, Others*	*Unknown*
Nephrotic syndrome	*Various cancers*	*Tumor antigens, immune complexes*