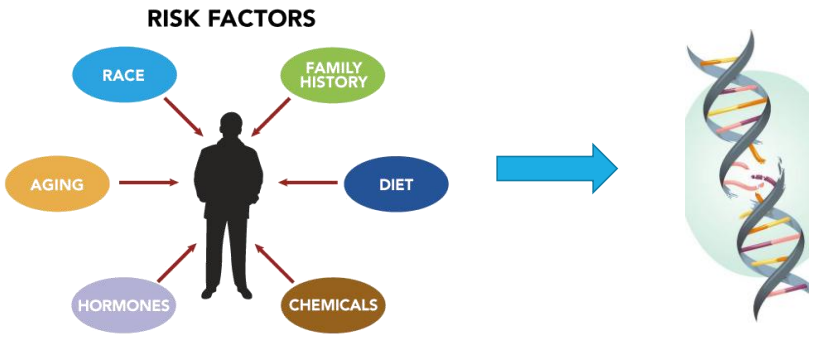
Introduction-1

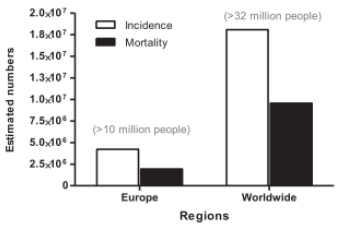
Goal

As chemical exposures and cancer rates increase worldwide, there is a need for students, researchers, public health professionals, and physicians to understand the mechanisms connecting exposure with human cancer risk.



Introduction

Cancer is a key public health concern, being the second leading cause of worldwide morbidity and mortality after cardiovascular diseases.



At the global level, cancer prevalence, incidence and mortality rates are increasing.

Several interrelated causes contribute to the high cancer incidence in Europe

These include:

1. lifestyles typical of industrialized countries
2. High urbanization and dense distribution of the aged population, with long-term exposure to occupational and environmental carcinogens and medicines
3. Chronic exposure to particulate matter, ozone, benzo[α]pyrene, and other pollutants that are above European standard limits and WHO air quality guidelines have been linked to a significant increase in respiratory NCD (Noncommunicable diseases) and cancers.
4. The early detection and screening programs (e.g. prostate or thyroid cancer) that contribute to a documented

Opportunities for carcinogenicity assessment to address the challenges of cancer disease and chemicals in the environment

- The safety assessment of carcinogenicity needs to evolve to keep pace with changes in the chemical environment and cancer epidemiology.
- Future strategies for assessing carcinogenicity based on a more holistic approach, can consider the prevalence of certain cancers, the study of relationships between chemical exposures and risk factors, the disease etiology and links with other disorders.
- In addition, changes in chemical exposure patterns and exposed populations are also critical considerations.

Historical Perspective

In 1775, Percival Pott described the increased incidence of cancer of the scrotum among chimney sweeps and attributed this to their contact with soot.

This was the first clinical report of occupational chemical carcinogenesis.

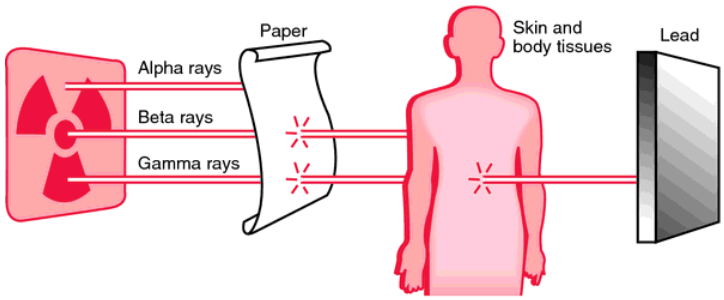
Historical Perspective (cont.)

Several compounds containing metals, such as nickel, chromium, beryllium, arsenic, coal and petroleum products, and asbestos, were thought to be responsible for the higher incidence of lung cancer in occupational environments.

Similarly, leukemia was associated with benzene and ionizing radiation from radon and radium.

Bladder cancer in the workplace was associated with the manufacture of aniline dyes, such as magenta and auramine.

❖Radiation with enough energy to knock electrons out of atoms and produce ions; is called ionizing radiation and includes alpha particles, beta particles, x-rays, and gamma-rays.



Historical Perspective

- Increased incidences of skin cancer are associated with exposure to chemicals generated from materials containing coal, petroleum, shale, and arsenic as well as from radiation.
- In 1915, skin cancer was induced on rabbit ears by painting them with coal tar.
- Similar results were obtained with other animal species using a variety of mixtures from coal and petroleum.

Historical Perspective (cont.)

Benzo(α)pyrene, a strongly carcinogenic compound that has been used as an indicator of carcinogenic potency, was isolated from coal tar in 1933.

Historical Perspective (cont.)

Several experiments were carried out in the 1930s and 1940s using polycyclic aromatic hydrocarbons (PAHs) and aromatic amines, which produced cancer in a variety of animal species.

Present Day Knowledge

World Health Organization

International Agency for Research on Cancer
World Health Organization

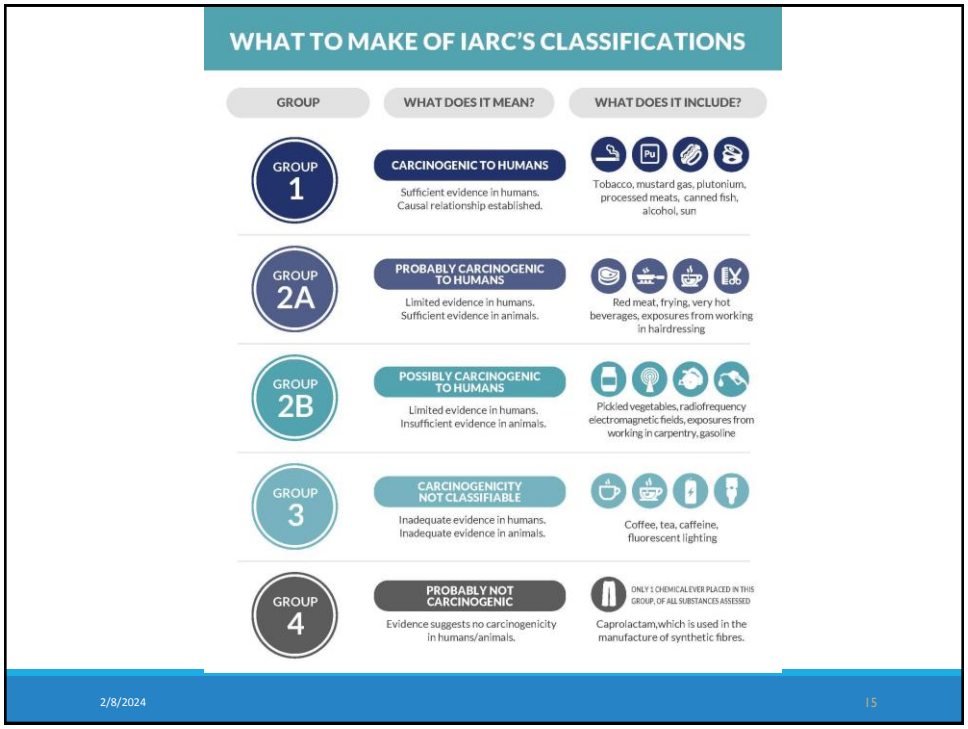
- As a part of the World Health Organization (WHO), the International Agency for Research on Cancer (IARC) in Lyon, France, was created.

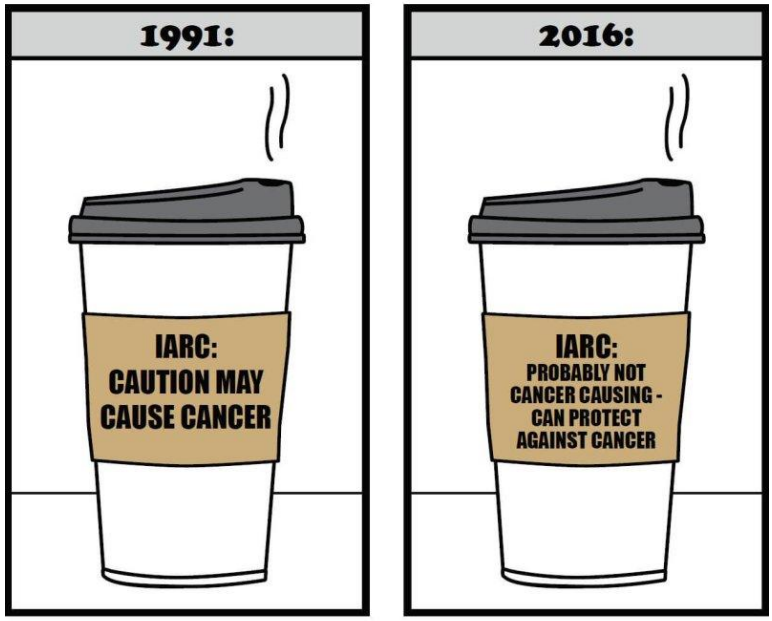
Present Day Knowledge

- In accordance with the procedures adopted as standard IARC practice, the agents, mixtures, and exposures as evaluated are classified into four groups:

1. Carcinogenic to humans,
2. (a) Probably carcinogenic to humans;

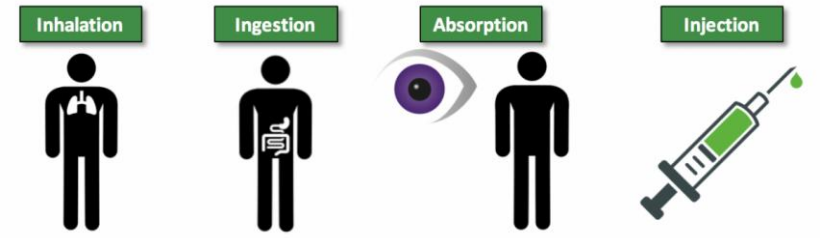
   (b) Possibly carcinogenic to humans,
3. Not classifiable as carcinogenic to humans,
4. Probably not carcinogenic to humans.


WHAT TO MAKE OF IARC'S CLASSIFICATIONS
GROUP
WHAT DOES IT MEAN?
WHAT DOES IT INCLUDE?
GROUP 1
CARCINOGENIC TO HUMANS
Sufficient evidence in humans. Causal relationship established.
Tobacco, mustard gas, plutonium, processed meats, canned fish, alcohol, sun
GROUP 2A
PROBABLY CARCINOGENIC TO HUMANS
Limited evidence in humans. Sufficient evidence in animals.
Red meat, frying, very hot beverages, exposures from working in hairdressing
GROUP 2B
POSSIBLY CARCINOGENIC TO HUMANS
Limited evidence in humans. Insufficient evidence in animals.
Pickled vegetables, radiofrequency electromagnetic fields, exposures from working in carpentry, gasoline
GROUP 3
CARCINOGENICITY NOT CLASSIFIABLE
Inadequate evidence in humans. Inadequate evidence in animals.
Coffee, tea, caffeine, fluorescent lighting
GROUP 4
PROBABLY NOT CARCINOGENIC
Evidence suggests no carcinogenicity in humans/animals.
ONLY 1 CHEMICAL EVER PLACED IN THIS GROUP, OF ALL SUBSTANCES ASSESSED
Caprolactam, which is used in the manufacture of synthetic fibres.


1991:
IARC:
CAUTION MAY
CAUSE CANCER
2016:
IARC:
PROBABLY NOT
CANCER CAUSING -
CAN PROTECT
AGAINST CANCER

1. Carcinogenic to humans
Asbestos Mustard gas 2-Naphthylamine Nickel refining Soots, tars, and mineral oils
2. Probably carcinogenic for humans
Beryllium compounds Carbon tetrachloride Cadmium and certain cadmium compounds
3. Not classifiable as to carcinogenicity to humans
Chloroprene DDT Dieldrin Hematite Isopropyl oils Lead and certain lead compounds

- The route of absorption of an agent is dependent on both its physical and chemical properties and the route of exposure.
- Inhalation is the most frequent route of exposure to vapors and fumes while skin is the route of absorption for both liquids and gaseous agents.
- Ingestion can also occur, particularly with agents in the solid phase.
- In different species the same organs may not be affected by the same agent.



How is chemical carcinogenicity determined?

Human Epidemiologic Studies **Animal studies**

- Human Epidemiological Studies determine the relationship between a cancer suspect chemical and a human population over a long period of time.

Lung cancer
e.g. Cigarette smoke

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How is chemical carcinogenicity determined?

- Animal studies directly induce cancer in test animals using a large sample of animals, usually of two or more species with varying dose and time parameters.
  - Experiments with animals are based on the premise that chemicals that produce cancer in animals will have similar effects on human cells.

Most substances known to be carcinogenic in humans Cause cancer in at least one animal.

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The rules that related both methods depend on certain scientific phenomenon as follow:

- For several carcinogens, the dose that cause cancer in human and lab animals is reasonably similar.
- Toxicity of chemical carcinogen in human is up to 10 times more sensitive that lab animals.

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Certain scientific phenomenons:(cont.)

- Smaller animals metabolize and excrete carcinogens more rapidly than larger animals.
- Human has (x 100) more susceptible cells than dose a mouse or rat.
- Life span of mans (x 35) times that of the mouse or rat → man more susceptible.

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Biochemical mechanisms of carcinogens and the basic biological facts:

- Carcinogenesis is dose-dependent

↑Dose → ↑tumor produce → shorter the lag time.

- Exposure (5-30 years) Development of tumor Long lag times
- No evidence for threshold dose →→value of dose of carcinogen which has no risk of cancer.

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Basic biological facts (cont.):

- Carcinogens can act transparently.
- Normal tissue → cancer by multistep process

Initiating agent are enhanced by promoting agents, hormonal agents &Other cofactors

- Cells in a state of rapid cellular proliferation → more susceptible to the action of carcinogen

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The same chemical carcinogen can cause:

- Tumors that are recognized differently by immune mechanisms in different individual

↓

Antigenic diversity

- Different types of tumors

↓

Diversity of phenotypes

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Biological mechanism of cancer development

- It take only one molecule of substance to genetically alter a cell → cancer
- Cancer is multistage process, that occurs over a period of year.
- It may take multiple exposures to several substances before a cancerous growth occurs.

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Dose-response assessment of a carcinogen

- Unlike the non-carcinogen, carcinogen has no threshold since it has an effect at any dose.
- This is due to the biological mechanism of cancer development.

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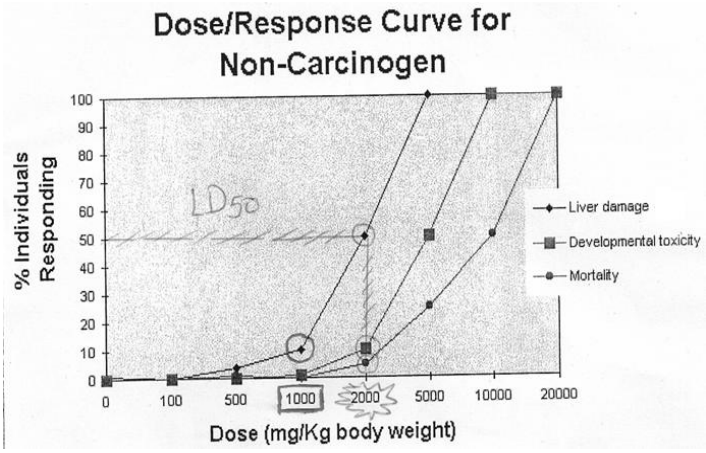

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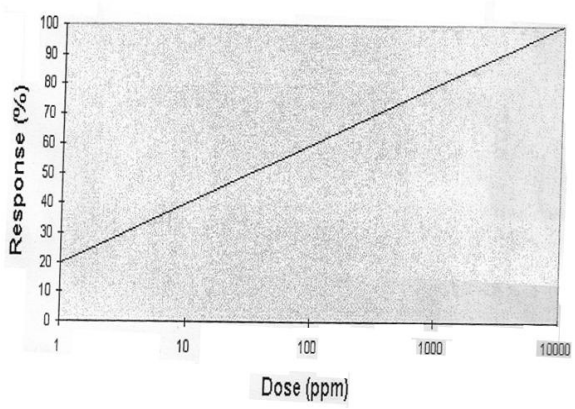
Dose Response curve for carcinogen



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What factors influence the development of cancer?

- **Dose--amount and length of exposure. The lower the dose you are to develop cancer. the least likely**
- **Environmental or "lifestyle" factors.**
  - ✓ Cigarette smoking (co-carcinogen)
  - ✓ Alcohol consumption (co-carcinogen)
  - ✓ Diet--high fat consumption, natural antioxidants
  - ✓ Geographic location--industrial areas, UV light
  - ✓ Therapeutic drugs--some are known carcinogens
  - ✓ Inherited conditions

Tumor and cancer (**)

- Cancer can be defined as an unregulated growth of cells arising from one cell.
- The scientific or medical term for cancer is malignant neoplasm, which is defined as a relatively autonomous growth of tissue not subject to the rules and regulations of normal growing cells.
- Tumor is a general term indicating any abnormal mass or growth of tissue. Therefore, a neoplasm is a tumor.

Neoplasm (Tumors)

- Neoplasm, New growth (Neos =New + plasma = thing formed) is an abnormal mass or colony of cells produced by autonomous (uncontrolled) growth of tissue.
- It arises from the uncontrolled proliferation of cells (or cell division).
- Most of the clonal expansion of a single cell has undergone neoplastic transformation.

Neoplasm (Tumors) (cont.)

- The transformation of a normal to a neoplastic cell can be caused by a chemical, physical, or biological agent that irreversibly alters the cell genome.
- Neoplastic cells pass on their heritable biological characteristics to progeny cells.
- Neoplasia is a general term that means tumor growth.

Tumor and cancer (cont.)

- Major features of benign tumors are encapsulation, slow growth, and non-invasion of surrounding tissue; that is, lack of metastasizing ability.
- Malignant tumors grow rapidly, are not encapsulated and invade surrounding tissue and metastasize.
- Benign growths generally have a normal complement of chromosomes, exhibit good differentiation, and have rare cell division. The opposite is characteristic of malignant neoplasms.

Tumor and cancer (cont.)

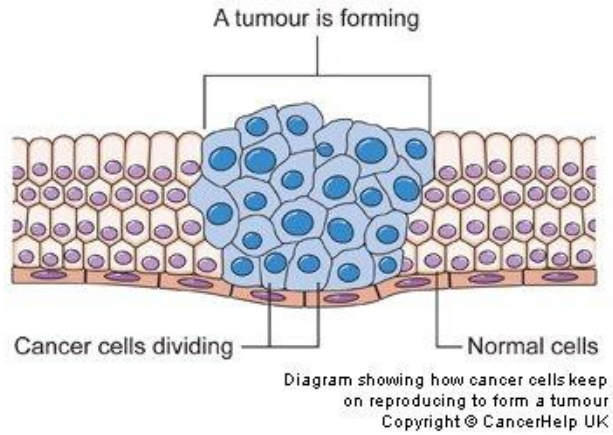

Diagram showing how cancer cells keep on reproducing to form a tumour
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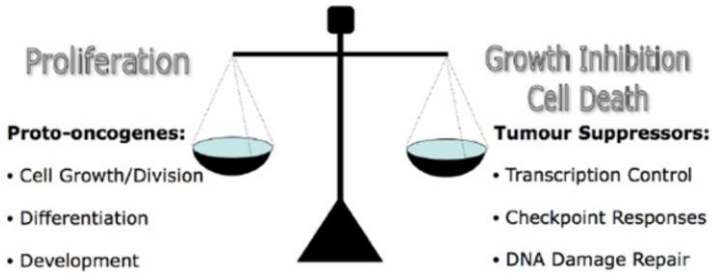
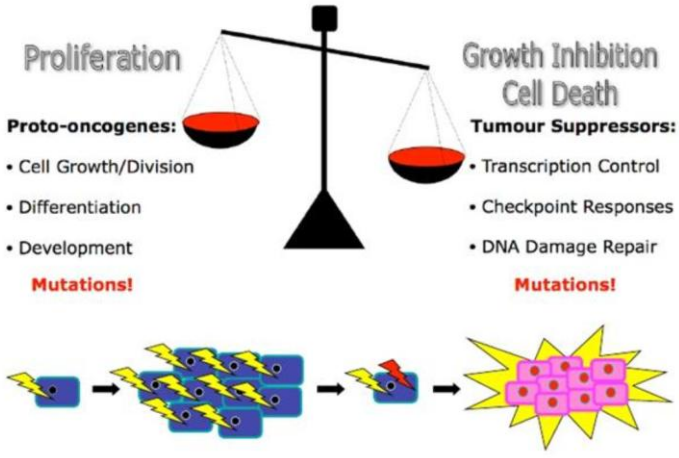
Healthy cell



Imbalance as number of mutations increase

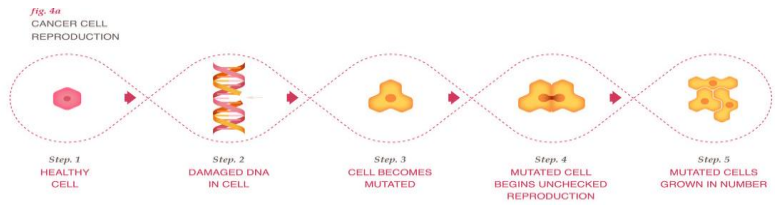


Comparison between the characteristics of normal and cancer cells

Normal cells	Cancer cells
✓Reproduce themselves exactly	✓ They don't die if they move to another part of the body
✓Stop reproducing at the right time	✓ Cancer cells don’t stop reproducing
✓Stick together in the right place	✓ Cancer cells violate signals from other cells
✓Self destruct if they are damaged	✓ Cancer cells stay immature and don’t specialize
✓Become specialized or 'mature‘	✓ Cancer cells do not stick together.
✓Show specific and normal functioning	

Cancer

Cancer is a group of diseases that occur when cells in the body become abnormal and have the potential to spread and establish growth in nearby tissues and other parts of the body. (Malignancy)



Classification of Cancer

- Carcinoma
- Sarcoma
- Leukemia
- Lymphoma
- Blastoma / Meningioma

Classification of Cancer (cont.)

Carcinoma

- These tumors are derived from epithelial cells (cells that cover surfaces, for example, cells of the skin, the lining of the digestive tract, and the gland). Epithelia are actively dividing.
- They include cancers of the breast, skin, and most internal organs.
- Malignant tumors of glandular tissue are also carcinoma but are called **adenocarcinoma**.
- Common forms of adenocarcinoma include breast, stomach, prostate, lung, pancreatic, and colorectal cancers.
- Carcinomas account for most of the cancers (85%).

Classification of Cancer (cont.)

Sarcoma

- These are the malignant tumors of mesenchyme or connective tissue.
- They include tumors of the muscle, bone and adipose tissues.
- Sarcomas are rare (about 8%) because these cells do not reproduce often.

Classification of Cancer (cont.)

Leukemia

The primary neoplasm is not a solid tumor but rather this form of cancer is characterized by an uncontrolled proliferation of leukocytes (white blood cells) and lymphocytes by either the bone marrow or lymphoid organs.

Classification of Cancer (cont.)

Lymphoma

Solid malignant cancers of the lymphoid or lymphatic organs (a system that cleans the blood), particularly the spleen and lymph nodes.

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Classification of Cancer (cont.)

Blastoma / Meningioma

These are the tumors of nervous tissue or nerve cells.

Tumors of the neurons appear in the embryo or very shortly after birth and are called **neuroblastomas**.

If these tumors arise from specialized nerve cells of the eye (retina) they are called **retinoblastomas**.

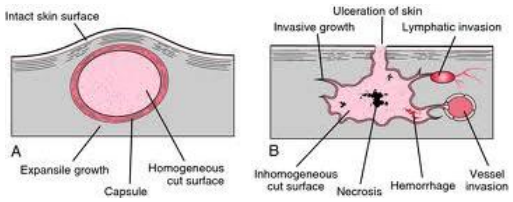
Other tumors of the brain and spinal cord arise from supporting cells; for example, cancers of cells covering the brain (meninges) are known as **meningiomas**

Types of Tumor

Tumor (neoplasm) -> new growth

Is any swelling or mass of tissue occupying a volume space. It has two types:

- **Benign tumors**
- **Malignant tumors**



Tumor Types (Benign)

- Benign tumors may arise in any tissue, grow locally, and cause damage by local pressure or obstruction.
- They form if the growth of cells is retarded by the formation of a fibrous capsule that localizes the effects of cancer cells and limits disruption of the general metabolism of the body.
- They are not generally life-threatening however benign brain tumors can cause death due to the build-up of pressure in the skull cavity and the risks of the associated surgery.
- They have a close structural and functional resemblance to normal tissues and cells and are termed well differentiated.
- They are usually separated from surrounding normal tissue by a capsule of connective tissue and do not spread to distant sites.

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Tumor Types (Malignant)

- They may arise in any tissue.
- Malignant neoplasms are more abnormal structurally and show less similarity to normal adult tissues (undifferentiated or less differentiated).
- Malignant tumors have no well-defined capsule and tumor cells grow in disorganized form.
- The most distinguishing features of malignant neoplasms are invasive growth and metastatic spread to other parts of the body.

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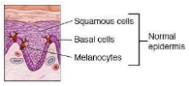
Benign Vs Malignant Tumors

	Benign	Malignant
Structure	Resemblance to normal cells (well differentiated)	Abnormal; less similarity to normal cells (undifferentiated)
Mitoses	Few	Relatively common
Growth	Usually purely expansive	Invasive
Growth rate	Slow	Rapid
Growth duration	May cease growing	Rarely cease growing
Encapsulation	Usually	Rarely
Metastasis	None	Frequent
Effect on host	Slight harm, due to location or complication	Significant harm, due to invasion and metastasis

Examples of Benign & Malignant tumors



Tissue	Basic cell type	Benign tumor	Malignant tumor
Tumors of epithelium			
Skin	Squamous epithelium Basal cell Pigment cell	Papilloma Nevus	Squamous carcinoma Basal cell carcinoma Malignant melanoma
Alimentary tract (lips, mouth, tongue, esophagus)	Squamous epithelium	Papilloma	Squamous carcinoma
Stomach, bowel	Columnar epithelium	Papillary adenoma	Carcinoma
Nasopharynx, larynx, lungs	Bronchial epithelium	Adenoma	Carcinoma
Urinary bladder	Transitional epithelium	Papilloma	Carcinoma
Solid epithelial organs (liver, kidney, prostate, thyroid, pancreas, pituitary etc)	Specific epithelium	Adenoma	Carcinoma

Examples of Benign & Malignant tumors (cont.)

Tissue	Basic cell type	Benign tumor	Malignant tumor
Tumors of mesenchyme			
Fibrous tissue	Fibrocytes	Fibroma	Fibrosarcoma
Fat	Adipocytes	Lipoma	Liposarcoma
Bone	Osteocytes	Osteoma	Osteosarcoma
Cartilage	Chondrocytes	Chondroma	Chondrosarcoma
Smooth muscle	Smooth muscle cell	Leiomyoma	Leiomyosarcoma
Striated muscle	Muscle cell	Rhabdomyoma	Rhabdomyosarcoma
Blood vessels	Endothelium	Haemangioma	Haemangiosarcoma
Lymph vessels	Endothelium	Lymphangioma	Lymphangiosarcoma

Examples of Benign & Malignant tumors (cont.)

Tissue	Basic cell type	Benign tumor	Malignant tumor
Tumors of nervous system			
Neurons	Nerve cells Nerve cells of eye		Neuroblastoma Retinoblastoma
Supporting cells	Astrocytes		Astrocytoma
Covering cells	Meningeal cells		Meningioma

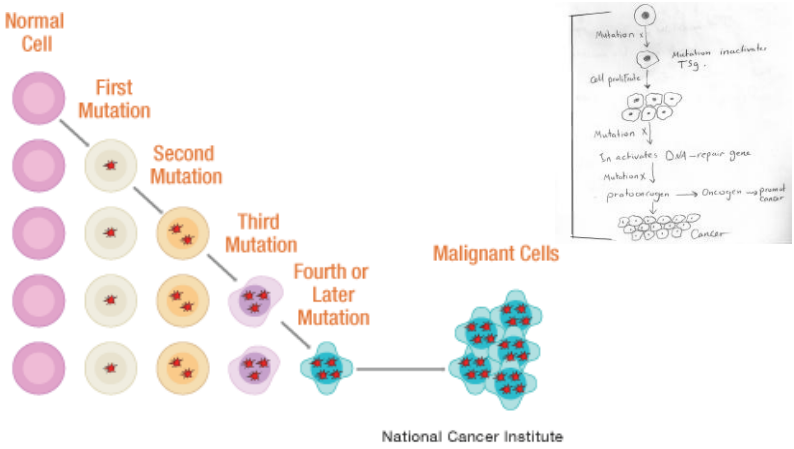
Examples of Benign & Malignant tumors (cont.)

Tissue	Basic cell type	Benign tumor	Malignant tumor
Tumors of reticuloendothelial system			
White blood cells	Myeloid cells		Myeloid leukemia
Red blood cells	Erythrocytes		Erythroleukemia
Lymphocytes	Lymphocytes		Lymphatic leukemia
Lymph nodes	Lymphocytes Fixed reticuloendothelial cells		Non-Hodgkin's lymphoma Hodgkin's disease

Steps of Cancer development

1. A series of Several Mutations is required before a cell be a cancer cell. This process involves:
2. **Oncogenes** → Promot cancer and are switched on by mutation.
3. **Tumor suppressor genes** → genes that prevent cancer and switched off by mutation.
4. **E**ach mutation alters the behavior of the cell to some extent.

A series of mutation is required before a cell be cancer cell

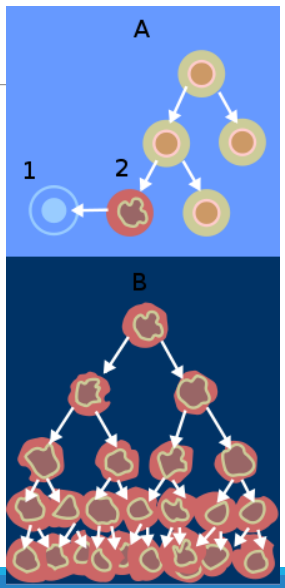


Normal cells

If its old or damage and not repair undergo apoptosis (programmed cell death).

Cancer cells

Avoid apoptosis by Mutation in DNA in cancer appear to disrupt apoptosis.



How cancer grows and spread:

A. Hyperplasia:

- Refers to tissue growth based on an excessive rate of cell division where cell structure and arrangement of cells remain normal, and the process is potentially reversible.
- There are two types of hyperplasia:

1)Physiological 2) Pathological

How cancer grows and spread(cont.)

Types of Hyperplasia:

1)Physiological

- Normally induced.

e.g.granular epithelium in female breast at puberty.

2)Pathological

- is caused by excessive hormonal stimulation.

e.g., in endometrium where hormonal imbalance led to bleeding → Heavy menstrual periods.

How cancer grows and spread(cont.)

B. Dysplasia:

- Is abnormal type of excessive cell proliferation that remain in original location.
- Characterized by loss of tissue arrangement and cell structure for e.g. "Carcinoma insitu" (insitu: "in place").
- It may develop into an invasive, metastatic malignancy

How cancer grows and spread(cont.)

C) Metaplasia:

An adaptive response to stress in which cell type is replaced by another, for protective from damage. E.g: Normal ciliated columnar epithelium replace by stratified Squamous epithelium.