# CANCER

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- **Cancer** is a genetic disease characterized by uncontrolled cell division and metastasis.
- There are two types of tumours.

1. The first type known as cancer or malignant tumour is characterised by invasiveness and metastasis.

2. The second type known as benign or non-cancerous tumour is localised.

- Tumours are monoclonal growth rather than polyclonal. Biochemical and genetic markers studies on tumour populations show that cells in a tumour populations are identical.
- It is believed that between 2-6 genes mutations to certain genes, specially those that control cell growth and division, are required for a cell to be transformed to malignant ones.
- Many cancers form solid tumors while others do not form solid tumors like cancers of the blood, such as leukemias.
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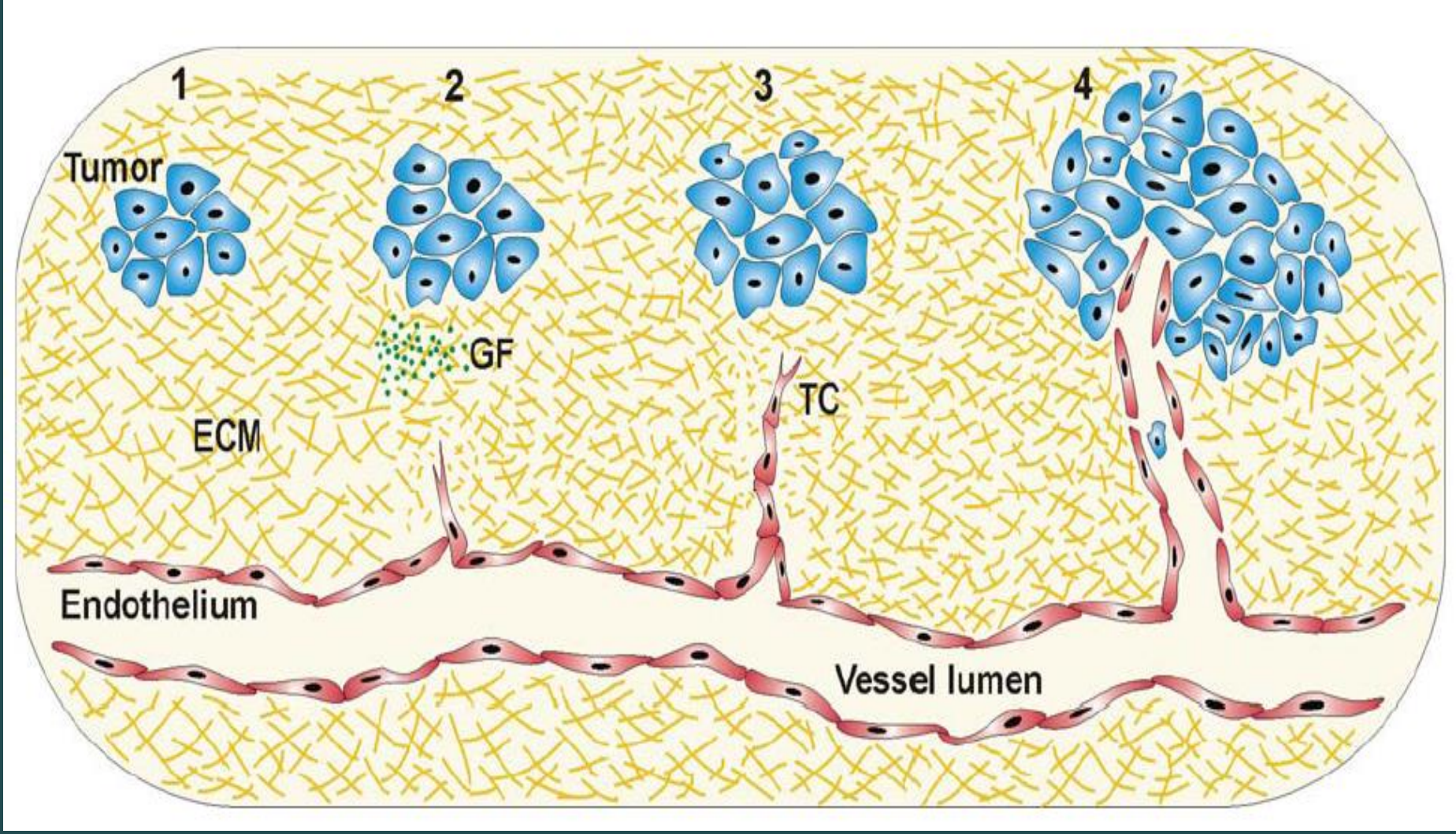
**Normal human cells undergo six alterations to be transformed into malignant cancer cells:**

- (1) Generation of own growth signal
- (2) Resistance to growth inhibition
- (3) Ability to escape apoptosis
- the life or death of a cell relies on signals received through survival receptors such as IGF-1R and IL-3 present on the surface of the cell and the death receptors FAS and TNF$\alpha$. Disruption of the FAS death receptors and mutation of p53 and other tumour suppressor genes play a crucial role in the cancer cell avoiding apoptosis.
- (4) Uncontrolled proliferation, resistance to growth inhibitor, the ability to generate their own growth signal and escape of apoptosis, all lead to uncontrolled proliferation of cancer cells.
- (5) Induction and sustainment of angiogenesis, the process of formation of new blood vessels in a tumour is known as angiogenesis. Angiogenesis is important for delivery of nutrients to tumour cells and progression of a pre-malignant lesion to a fully invasive tumour.

# Angiogenesis



(6) Metastasis and invasiveness: Metastasis refers to the ability of the cancer cells to spread away from the primary tumour and invade other parts of the body.

- There are two main events in metastasis.

**1- Changes in attachment of cells**

- Cells produce adhesion substances including

A-The integrins is involved in cell to extracellular matrix (ECM) interaction whereas

B-The **cadherins** is involved in cell to cell interaction. Cadherins are mutated in most of the epithelial cancers and this plays a crucial rule in enhancing invasiveness and metastasis.

2- **Activation of extracellular proteases** that degrade the extracellular matrix (ECM).

The activation of extracellular protease facilitates the invasion of cancer cells by promoting degradation of ECM.

- **Cancer cells characteristics**
- Tumour cells differ from normal cells in a number of characteristics including:

(1) Cell size: Tumour cells are either abnormally large or abnormally small compared to normal cells,

(2) Nuclear size: Nuclear size in tumour cells is **much larger** than that in normal cells and it has irregular chromatin distribution,

(3) Ability to grow in suspension: Unlike normal cells the tumour cells are able to grow in suspension

(4) Specialization: Cancer cells are less differentiated than normal cells. Thus cancer cells are less specialized than normal cells with no specific functions.

# The risk factors for cancer include

1- **Environment**:

It is estimated that environmental factors are responsible for 80%-90% of cancer

- Environmental factors include smoking (30%), diet (30%), infection 15-20% and the remaining is due to radiation, stress, viruses, environmental pollutant etc.

2- **Hereditary**:

❖ About 5-10% of cancer can be related to inherited genes.

❖ It is estimated that about two third of cancer can be prevented through changes in life style including avoidance of smoking and drinking, and dietary alterations.

# Viruses and cancer

It is believed that cervical carcinoma, hepatomas (liver cancer), some head and neck cancer, kaposi's sarcoma (herpesvirus 8 (HHV8)) , some anal cancers, and Burkitts lymphoma are caused by viruses.

99.7% of cervical tumours have fragments of papilloma virus genome integrated to the host cell genome.

The virus can cause direct oncogenetic changes by numerous mechanisms including:

- Providing oncogenes to a normal cell
- Inhibiting tumour-suppressor gene function
- Enhancing DNA damage
- Inhibiting apoptosis of damaged cells
- Interfering with DNA repair mechanisms
- Resisting host organism immune effector mechanisms.

# Cancer Classification

Cancers are classified in two ways:

1. The location in the body where the cancer first developed known as primary site.
2. The type of tissue in which the cancer originates (histological type)

## Cancer classification based on histological type.

From a histological point cancers are classified into six major categories:

1. Carcinoma
2. Sarcoma
3. Myeloma
4. Leukemia
5. Lymphoma
6. Mixed Types

## 1. Carcinoma

They are formed by epithelial cells which covers the inside and outside (skin) surfaces of the body.
Carcinomas are the most common type of cancer that account for 80 to 90 percent of all cancer cases.

Carcinomas are divided into two major subtypes:

A. Adenocarcinoma: cancer that begins in glandular (secretory) cells such as mucus, digestive juices, or other fluids.

B. Squamous cell carcinoma: squamous cells are found in the tissue that forms the outermost layer of the skin (epidermis), the lining of the hollow organs of the body, and the lining of the respiratory, digestive tracts and urinary tract.

## 2. Sarcoma

Sarcoma refers to cancer that originates in supportive and connective tissues such as bones, tendons, cartilage, muscle, and fat.

Examples of sarcomas are:

Osteosarcoma or osteogenic sarcoma (bone)

Chondrosarcoma (cartilage)

Fibrosarcoma (fibrous tissue)

## 3. Myeloma

Myeloma is cancer that originates in the plasma cells of bone marrow.

Often called multiple myeloma because most people (90%) have multiple bone lesions at the time it is diagnosed.

Plasma cells are a type of white blood cells that secrets antibodies. When these abnormal plasma cells spread throughout the bone marrow so that there is not enough space to make enough normal blood cells decreased numbers of-red blood cells, white blood cells, and platelets.

## 4. Leukemia

also known as blood cancer that begin in the blood-forming tissue of the bone marrow are called leukemias.
Leukemia is often associated with the overproduction of immature white blood cells therefore the patient is often prone to infection.
Leukemia also affects red blood cells and can cause poor blood clotting and fatigue due to anemia.

## 5. Lymphoma

Lymphoma is a cancer of the lymphatic system which is part of immune system. The lymphatic system includes the lymph nodes (lymph glands), spleen, thymus gland and bone marrow.

## 6. Mixed Types

A **mixed tumor** is a tumor that derives from multiple tissue types.  Example: carcinosarcomas which is mixture of carcinoma and sarcoma

# Cancer Genetics

The genes involved in the development of cancer are classified into:

**1- Proto oncogene (oncogene)**

**2- Tumour suppressor genes**

## 1- Proto oncogene and oncogene (gain of function)

- Proto-oncogenes function is to promote cellular growth, proliferation, and differentiation.
- When cell growth is completed, proto-oncogenes are turned off.

- Proto-oncogenes code for **growth factors, growth factor receptors, signal transduction proteins, intracellular kinases, and transcription factors.**

- Oncogenes are the mutated forms of proto-oncogenes that promote overproduction of growth factors or increase their activity.
- Oncogenes also disrupt the activity of cyclins and cyclin-dependent kinases (CDKs); disruption of cyclin-dependent kinases distracts the cell cycle checkpoint leading to uncontrolled cell division of the mutated cells.

## Proto-oncogenes and oncogenes

- Proto-oncogenes get converted to oncogenes through
- 1. Mutation, 2. Translocation; 3. Gene amplification

- **1. Mutation:** could occur in two sites in proto-oncogenes
- (a) Mutation in the regulatory region that may result in increasing the rate of production of the proto-oncogene protein. or
- (b) Mutation in the coding portion of the gene that results in the synthesis of a protein capable of transforming the cell.

## 2. Translocation

- The entire proto-oncogene or a portion of it may be translocated, that is, moved from one position in the genome to another.
- In its new location, the proto-oncogene may be controlled by a more active promoter and, therefore, overexpressed
- If only a portion of the proto-oncogene is translocated, it may be expressed as a truncated protein (shortened protein) with altered properties, or it may fuse with another gene and produce a fusion protein containing portions of what normally were two separate proteins.
- The truncated or fusion protein would be hyperactive and cause inappropriate cell growth.
- For example, in Burkitt's lymphoma the MYC gene initially found at chromosome 8 is translocated to chromosome 2, 14, or 22.

## 3. **Gene amplification**

- Gene amplification occurs when a certain region of the chromosome undergoes several rounds of DNA synthesis in the same cell cycle.
- Cancer has always been found to be associated with amplifications of oncogenes.
- For example, ERBB2 amplification is always found in breast and ovarian cancers.

# Two common oncogenes are:

1. **HER2 gene (human epidermal growth factor receptor 2) also known as ERBB2 gene**, a gene that produces a protein found on the surface of all breast cells.

- HER2 receptors function: it help control how a healthy breast cell grows, divides, and repairs itself.

- **HER2** mutation causes protein overproduction which is associated with breast cancer.

2. **The RAS family of genes**, a family of genes that make proteins involved in cell signaling pathways that control cell growth and cell death.

- **2- Tumour suppressor genes**
- Tumor suppressor genes encode proteins that inhibit proliferation, promote apoptosis , and repair DNA.

- Tumour suppressor genes regulate many functions in cells including cell cycle, recognition of DNA damage and its repair and protein degradation.

- In tumour suppressor genes, only one allele of the gene pair is enough to function as a suppressor. This means that to lose suppressor function both alleles of a tumour suppressor gene pair have to be mutated.
- The most known and studied tumour suppressor gene is p53. Other Examples of tumor suppressor genes include BRCA1 and BRCA2

# Cell Cycle Suppression and Apoptosis

- Normal cell growth depends on a balanced regulation of cell cycle progression and apoptosis by proto-oncogenes and growth suppressor genes.
- At checkpoints in the cell cycle the tumor suppressor genes slow growth in response to signals from the cell's environment, including external growth inhibitory factors, or to allow time for repair of damaged DNA, or in response to other adverse circumstances in cells.
- Cells with damaged DNA are targeted for apoptosis so that they will not proliferate.
- Apoptosis is initiated by either death receptor activation or intracellular signals leading to release of the mitochondrial protein the cytochrome c.

- **Example of tumour suppressor genes: p53**
- p53, often called the guardian of the genome
- p53 protein is made up of 393 amino acids and is not important for cell growth or development.
- However, p53 is a transcriptional factor that regulates the expression of more than one hundred genes.
- There are many internal and external stress signals that activate p53 including DNA damage, heat shock, metabolic change, cell-cell contact, and activated oncogenes.

- The main role of p53 in the cell is to regulate the cellular response to internal and external stress signals through regulation of cell cycle arrest and apoptosis. The regulations include cell cycle checkpoints, differentiation, and DNA repair.
- p53 is the most mutated gene in human cancer. It has been found that p53 has 75%-80% mutations or abnormalities in colon tumours alone and between 50-60% of all human cancers. Mutations in p53 lead to survival of cells with damaged DNA that may lead malignant transformation

# Genetic Testing for Cancer Risk

- Genetic testing helps estimate your chance of developing cancer in your lifetime.
- Through testing mutations in genes, chromosomes, or proteins

- Genetic tests are available for some types of cancer including:
- Breast cancer, ovarian cancer, colon cancer, thyroid cancer, prostate cancer, pancreatic cancer, melanoma, sarcoma, kidney cancer, and stomach cancer

- **Advantages of genetic testing:**

1. Predict the risk of a particular cancer
2. Find the possibility to pass the defective genes to children and increased their cancer risk
3. Steps to be take to lower the risk of cancer.

- For example: surgery, medication, frequent screening, or lifestyle changes.

- Genetic test for cancer is prediction not for sure for example a woman may have a 70% chance of breast cancer but may never develop the disease. Meanwhile, a woman with a 25% chance may develop breast cancer.

# Risk factors for hereditary cancer

The 3, 2, 1 criteria for hereditary cancer are:

- **1. Family history of cancer:** Having 3 or more close relatives that has the same or related forms of cancer.
- **2. Cancer at an early age:** Having 2 or more relatives diagnosed with cancer at an early age.
- **3. Multiple cancers:** When one relative develops 2 or more types of cancer.

# Example of Hereditary Cancer:

## Hereditary Breast and Ovarian Cancer (HBOC)

# Hereditary Breast and Ovarian Cancer (HBOC)

- There are 2 primary genes linked with breast cancer: ***BRCA1* and *BRCA2*** both are tumor suppressor genes.
- BRCA stands for BReast CAncer and they both help repair damaged DNA
- Men with these gene mutations also have an increased risk of breast cancer and prostate cancer.
- 55%–72% of women who inherit a mutated *BRCA1* variant and 45%–69% of women who inherit a mutated *BRCA2* variant will develop breast cancer by 70–80 years of age.
- 39%–44% of women who inherit a mutated *BRCA1* variant and 11%–17% of women who inherit a mutated *BRCA2* variant will develop ovarian cancer by 70–80 years of age.

- **How is HBOC identified**
- Genetic testing for hereditary breast and ovarian cancer looks for mutations in the *BRCA1* and *BRCA2* genes through a blood or saliva test.
- The usual method of testing, called **standard gene sequencing**, can find most *BRCA* mutations.

**How can HBOC be avoided to be passed to children's?**

- Preimplantation genetic diagnosis (PGD) along with in-vitro fertilization (IVF).
- When the embryos reach a certain size, 1 cell is removed and tested for the specific hereditary condition.

# Risk reduction in people with *BRCA* gene mutation

1. Breast cancer screening at younger ages

- No effective ovarian cancer screening methods are known.

2. Bilateral mastectomy, which is surgical removal of both breasts, can lower the risk of breast cancer by more than 90%.

- Only about 3% of breast cancers associated with *BRCA* mutations are diagnosed before age 30, so most women with a *BRCA* mutation could consider surgery after 30.

3. Salpingo-oophorectomy, which is the surgical removal of the ovaries and fallopian tubes, can lower the risk of ovarian cancer by approximately 90%. It may also help lower the risk of breast cancer by 50% for women who have not been through menopause.

# Cancer Diagnosis

**1. Biopsy:** This involves taking a sample of tissue from a potentially cancerous lesion and examine the cells for signs of cancer.

**2. Imaging scans:** Examples: computed tomography (CT scan), Ultrasound, or MRI scan.

**3. Tumor markers:** Cancerous cells release compounds into the blood. Lab tests can confirm a diagnosis.

- Alpha-fetoprotein (AFP) used as a marker for Liver cancer
- Bladder Tumor Antigen (BTA) used as a marker for Bladder cancer.

# Cancer- Staging

- Cancer is treated by surgery, radiation, Immunotherapy, hormone therapy and chemotherapy beside other ways. The choice of treatment depends on cancer stage, type, treatment success, and patient's age and health.
- **Staging:** is a system that defines the extent of cancer spread.
- **The Tumor Node Metastasis (TNM) staging system**: classify tumour into three categories T, N, & M.

(1) T represents the extent of primary tumour. Its size and spread to nearby tissue. It is divided into T1, T2, T3 and T4 depending on the extent of cancer. T4 is considered a massive lesion and in general it is hard to treat.

(2) N represents the effect of cancer on lymph nodes. It is sub-classified in to N0, N1, N2 and N3. In N3 the lymph nodes are fixed by the tumour to surrounding structures.

(3) M stands for metastasis. Presence of metastases is indicated by M+ and its absence is indicated by M-

# Cancer treatment

## 1. Surgery

- Surgery is the cornerstone of treatment for most solid cancers that are confined to the organ of origin. However, it may not deal with micrometastatic disease (Small numbers of cancer cells that have spread from the primary tumor to other parts of the body) and therefore chemotherapy or radiotherapy is often given before or after definitive surgery.

## 2. Radiation Therapy (Ionizing Radiation)

- Ionizing radiation damages cells by destroying DNA.
- Ionizing radiation can also damage water molecules in cells leading to the formation of reactive oxygen species (ROS). ROS produced cause DNA damage including strand breakage and loss of nucleobases.
- DNA damage leads to cell death through apoptosis or necrosis.
- Cancer cells does not die directly but takes few days or weeks to die

## 3. Immunotherapy to Treat Cancer

- Boost body's own immune system to prevent, control, and eliminate cancer through the use of many substances.

## Immunotherapy to Treat Cancer include the use of Vaccines:

**Cancer Vaccines** of two types:

### 1. Preventive Cancer Vaccines

- Cervical cancer and head and neck cancer can be caused by human papilloma virus, liver cancer can be caused by hepatitis B virus. Vaccines have been developed that can prevent human papilloma virus and hepatitis B virus.

### 2. Therapeutic Cancer Vaccines

- Help forcing the immune system to recognize a virus or cancerous cell. Example: the use of specific cancer antigens to force the immune system into action.

- **4. hormone therapy:**
- Some cancers like prostate and breast cancers depend on hormones to grow thus block patients body from making certain hormones or alter hormones can sometimes help slow or stop the growth of these cancers.

- **5. Chemotherapy**
- Chemotherapy involves the use of drugs to kill malignant cells.
- Chemotherapy works in many different ways including interacting with DNA, binding to cellular proteins such as tubulin, and interacting with DNA associated proteins.

- **Necrosis: i**s unregulated cell death due to cell injury resulting from internal or external stresses such as injuries, chemical agents, or pathogens.
- **Apoptosis:** is programed cell death (cell suicide) to eliminate unwanted cells or damaged cells beyond repair.