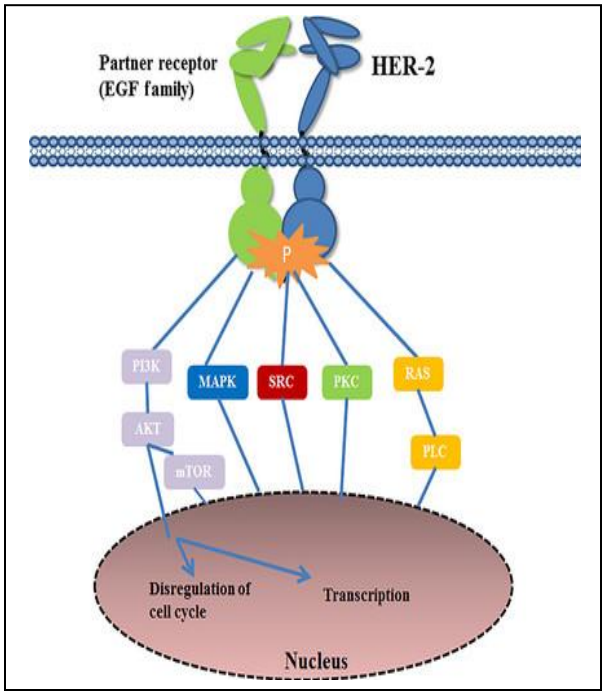
Cell numbers are a product of the rates of cell division (mitosis) and cell death (apoptosis). Cancer can arise as a result of gene mutations that affect the rate of mitosis as well as apoptosis, thereby leading to the accumulation of extra cells (cell accumulation disorders).

The cell cycle is controlled by proteins from inside and outside the cell:

1. Intracellular Cyclins and Cyclin Dependent Kinases (CDKs) control the checkpoints.
2. Extracellular proteins (called Growth Factors) or hormones from other cells signal target cell to divide. Examples **Fibroblast growth factors (FGFs)** are a family of proteins that are normally expressed during the proliferation of cells required for normal wound healing and **Platelet-derived growth factor (PDGF)** is a polypeptide that is normally important for extracellular matrix production.

Hormones (e.g. Growth Hormone) or Growth Factors (FGFs or PDGF) are bind to receptor proteins on a target cell membrane. This triggers a molecular signaling pathway. A series of linked proteins activate Cyclin- CDKs which Allows Cells to Pass Cell Cycle Checkpoints and divide.

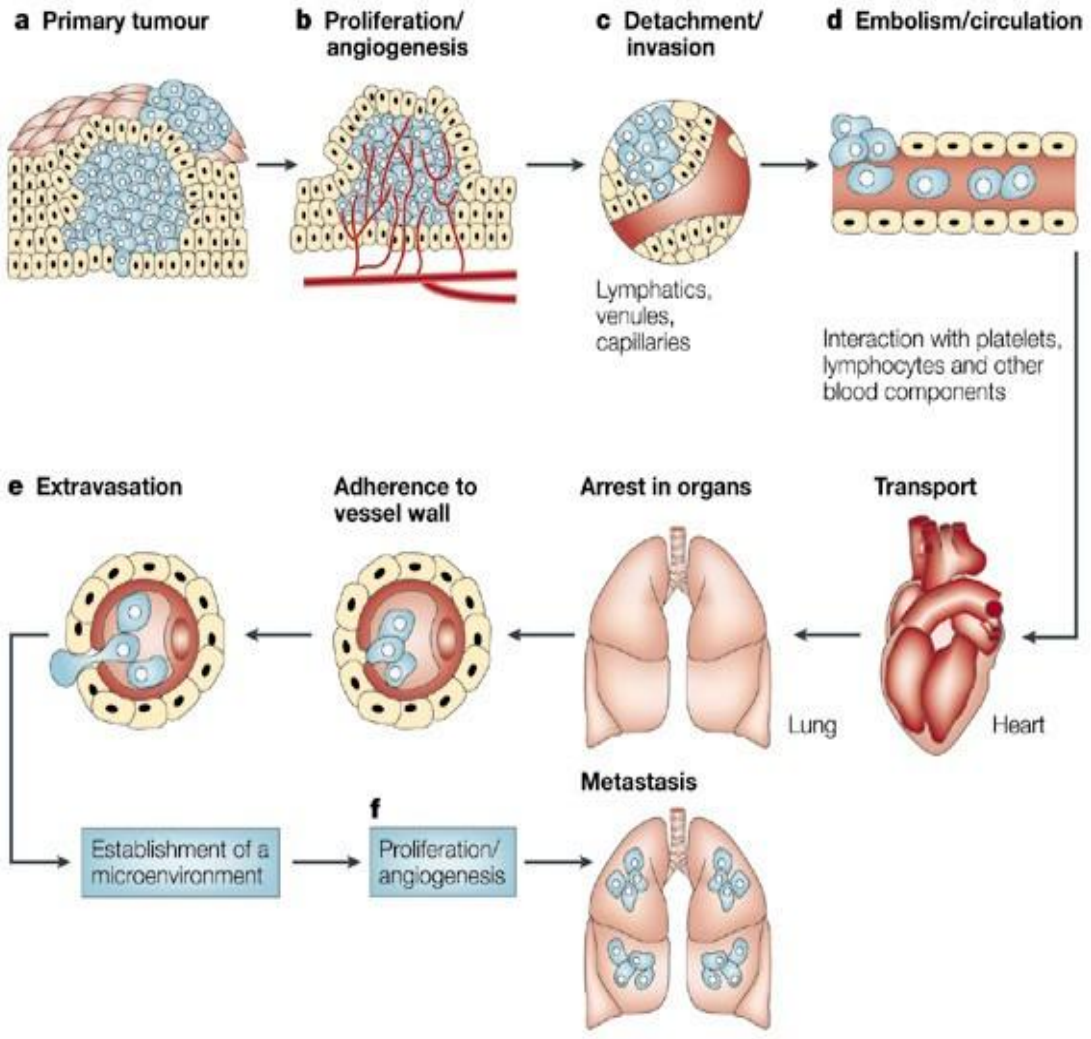
Overexpression of growth factors or growth factor receptors can lead to tumor formation. Overexpression of the growth factor **receptor** *erb b-1*, also known as HER2/neu, is associated with the development of breast cancers. Breast cancers are often responsive to **estrogen**. Therefore, once breast cancers have been shown to express estrogen receptors.



Cancer is a group of diseases caused by the uncontrolled multiplication of abnormal cells in the body, a process called **neoplasia**. Abnormal new tissues called **neoplasms** are formed. Neoplasms usually form masses called tumors that may be benign (non-cancerous) or malignant (cancerous). Malignant or cancerous tumors grow rapidly, are invasive to surrounding tissue and metastatic (traveling via blood/lymph to invade distant tissues).

Pathogenesis of Metastasis

Cells in a primary tumor develop the ability to escape and travel in the blood. Tumor cells secrete enzymes to break down extracellular matrix and gain access to blood vessels. In blood they can escape attack by immune cells by attaching to platelets. Tumor cells attach to capillary walls and secrete more enzymes to digest their way out, and grow in a new location (metastasis) forming a secondary tumor.



- Cancers are genetic disorders caused when cells are genetically altered via gene mutations or chromosome translocations. Inherited mutations give a predisposition for certain cancers. Only 10% of cancer is inherited, 90% is sporadic (Spontaneously occurring, not inherited), that is, the mutations are not inherited but occur during individual life.

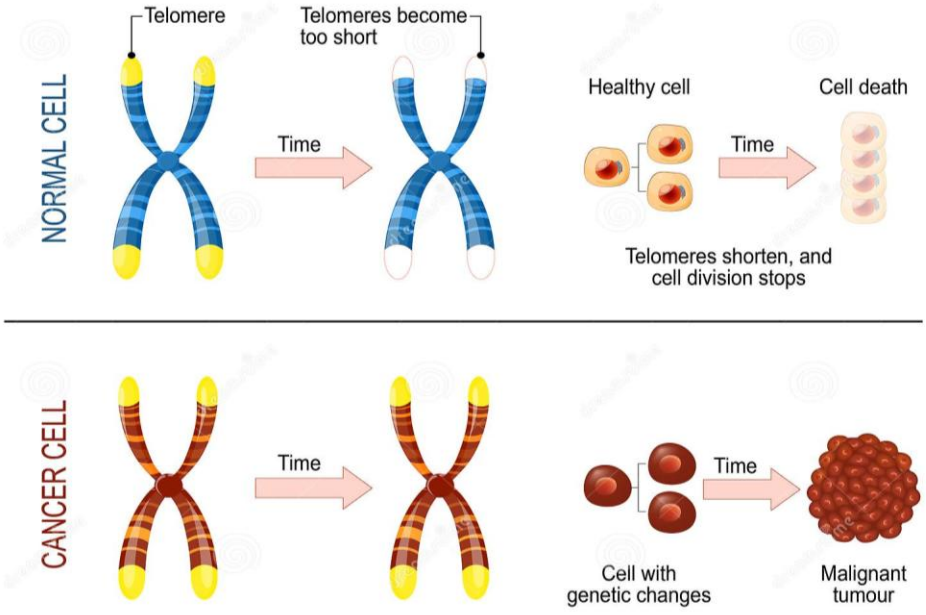
❖ Characteristics of Cancer Cells

Cancer cells have distinguished characteristic feature include:

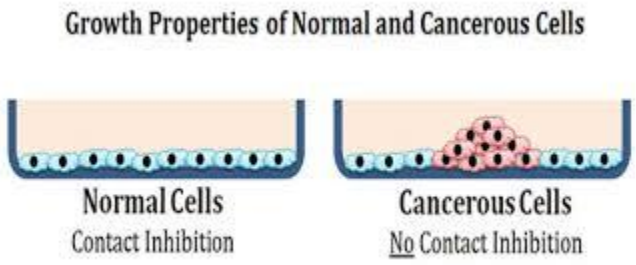
1. **Unlimited replication potential:** Ordinarily cells divide about 60 to 70 times and then just stop dividing and eventually undergo apoptosis. Cancer cells are immortal and keep on dividing for an unlimited number of times. Human chromosomes ends with special repetitive DNA sequences called **telomeres.** In a normal cell, the telomeres get shorter after each cell cycle and gradually decrease. When the chromosomes' ends to bind together, causing the cell to undergo apoptosis.

Telomerase is an enzyme that maintains the length of DNA rebuilds telomeres sequences so prevents a cell from ever losing its potential to divide.

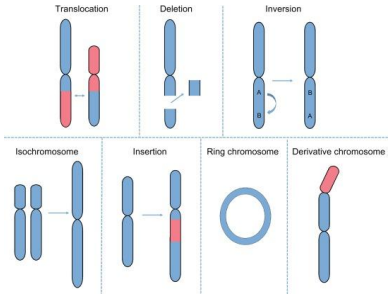
The gene that codes for telomerase is constantly turned off in normal cell but turn on in cancer cells, and telomeres are continuously rebuilt. The telomeres remain at a constant length, and the cell can keep dividing over and over.



2. **Genetically unstable** due to loss of DNA repair mechanisms (so are more susceptible to radiation damage than normal cells).
3. **Lose the contact inhibition** (meaning that when they come in contact with a neighbor, they stop dividing). Cancer cells have lost all restraint. They pile on top of one another and grow in multiple layers, forming a **tumour.**



4. Lose the normal attachment to other cells so become **metastatic** (travelling via blood/lymph to invade distant sites). Cancer cells make their way across the basement membrane and invade a blood vessel or lymphatic vessel by produce **proteinase** enzymes that degrade the basement membrane and allow them to invade underlying tissues.
5. **Secrete signals for angiogenesis**: (**Angiogenesis** is the formation of new blood vessels) tumors have a well-developed capillary network to bring it nutrients and oxygen.
6. **Lack of differentiation: (Differentiation** is the process of cellular development by which a cell acquires a specific structure and function) Cancer cells are none specialized and do not contribute to the functioning of a body.
7. **Abnormal Nuclei**: The nuclei of cancer cells are enlarged and may contain an abnormal number of chromosomes or often have chromosomal structural abnormalities. Some portions of the chromosomes may be duplicated, and/or some may be deleted.



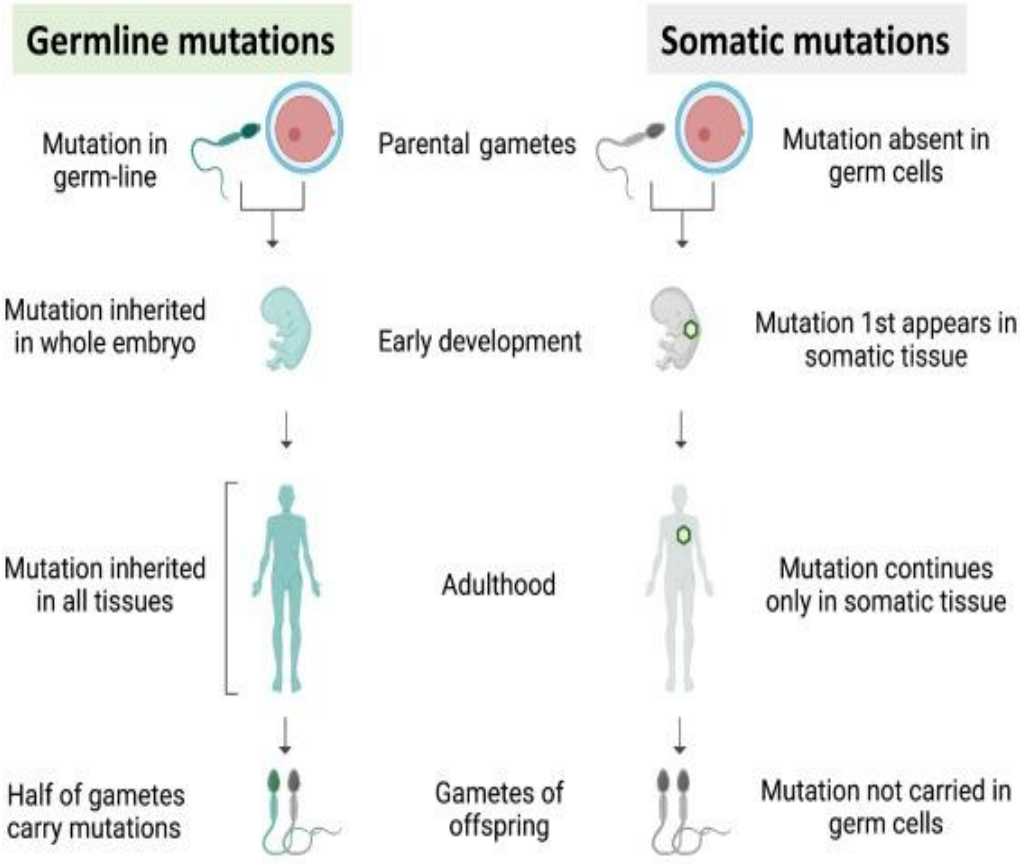
Causes of cancer

Inherited mutations in genes that affect cell cycle, DNA repair, or apoptosis: these mutations give a genetic predisposition for cancer.

Somatic mutations to these same genes caused by:

1. Exposure to risk factors such as environmental mutagens (carcinogenic chemicals, radiation), hormones and Weakening of immune system (as in AlDS).
2. Oncogenic (tumor) virus infections: eg Epstein Barr virus (causes Burkitt lymphoma) and Human Papilloma virus (causes cervical cancer).Tumor viruses transform human cells into cancer cells by Introducing viral cancer - causing oncogenes into host cell DNA or by Causing Translocation and overexpression of host proto-oncogenes.

- ✓ Carcinogens are cancer-causing agents.
- ✓ Mutagens are agents that change the genetic code in a cell.
- ✓ Almost all carcinogens are mutagens.



Mutations in 4 types of genes cause Cancer

1. **Proto - oncogenes**: genes that code for normal proteins used in cell division, growth factors, membrane receptors for growth factors, and signaling proteins.
   When proto-oncogenes mutate, they become cancer-causing genes called **oncogenes.** These mutations can be called "gain-of function," or dominant mutations. Each cell possesses two copies of each proto-oncogene, if only one copy be mutated the cell will lose control of the cell cycle. Where the gene is continually expressed resulting in overproduction of a protein that stimulates cell division (e.g. in Chronic Myeloid Leukemia) or by mutating to a form that is over expressed. Several proto-oncogenes code for **Ras** proteins that promote mitosis by activating cyclin. *Ras* oncogenes are typically found in many types of cancers**.** ***Cyclin D*** is a proto-oncogene that codes for **cyclin** directly. When this gene becomes an oncogene, cyclin is readily available all the time.

2. **Tumor Suppressor genes:** genes that code for proteins that help prevent uncontrolled cell division by bind to checkpoint proteins to stop the cell cycle and prevent cell division if DNA is damaged. Tumor suppressor proteins stop division of mutated cells until mistakes in DNA are repaired by enzymes. Tumor suppressor proteins keep most mutations from being passed on to daughter cells and developing into cancer. If the genes for Tumor suppressor proteins mutate the brake on cell division are removed cancers may result. Two important tumor suppressor proteins are the **p53** protein and the **RB** protein. The p53 tumor suppressor protein is activated when DNA is damaged. The *p53* gene is called the "guardian angel of the genome"P53 protein activates genes for proteins that Prevent cell entering S phase, Repair DNA and Cause apoptosis (if DNA is irreparable).
3. **Genes for Apoptosis:** ***Bax*** is a good example for apoptosis genes encoded to the protein Bax, promotes apoptosis. When *Bax* mutates, Bax protein is not present and apoptosis is less likely to occur.

4. **DNA Repair genes**: encoded for DNA repair enzyme such as alkytransferase, photolyase and dioxygenase. Most cancer cells have a deficiency of some DNA damage response pathways.

- ✓ **RAS is an abbreviation of "Rat sarcoma," reflecting how the first members of the RAS gene family were discovered over three decades ago. The RAS family is composed of 36 human genes, but KRAS, NRAS, and HRAS by far play the most prominent roles in human cancer**
- ✓ **The retinoblastoma (Rb) gene family which encode nuclear proteins (pRB) acting as negative regulators of cell proliferation, when in their dephosphorylated status. Alteration of Rb family members is frequently involved in gynecological cancers.**