Define Cancer

Cancer is a term used to describe a large group of diseases that are characterized by cellular malfunction.

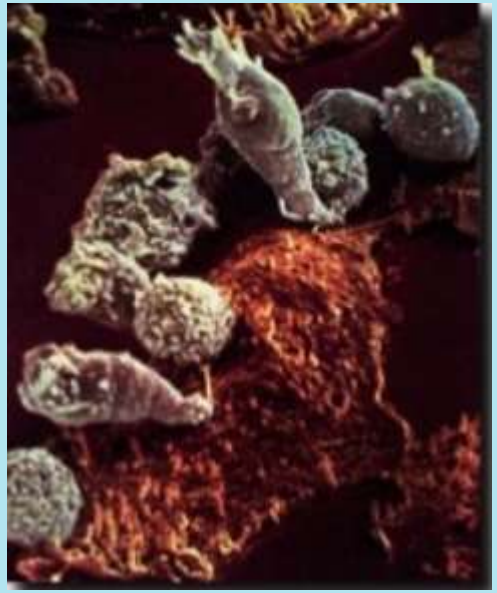
Healthy cells are programmed to “know what to do and when to do it”. Cancerous cells do not have this programming and therefore grow and replicate out of control. They also serve no physiological function. These cells are now termed as neoplasm.

Oncogenes

- **Oncogenes are mutated form of cellular proto-oncogenes**
- **Proto-oncogenes code for cellular proteins which regulates normal cell growth and differentiation**

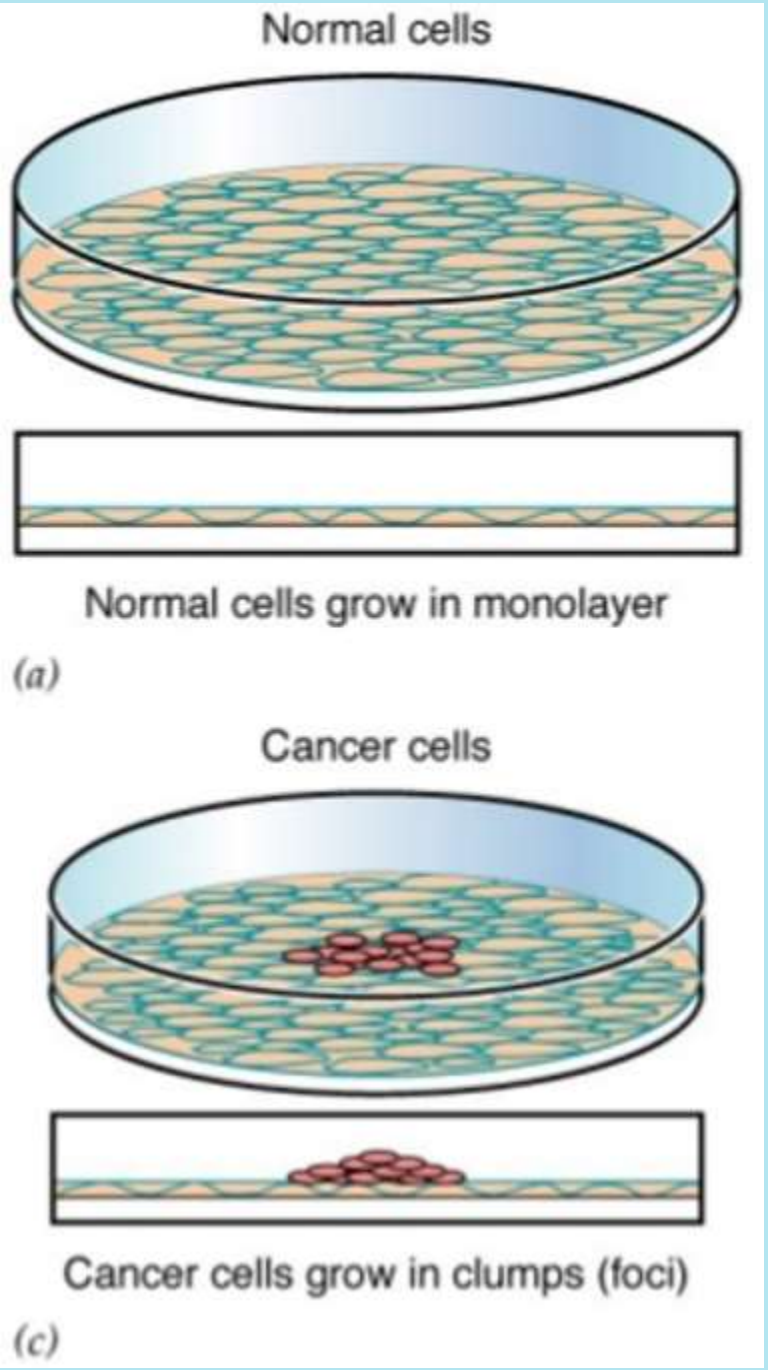
Normal Cells vs Cancer Cells

- **Cancer cells lose control over growth and multiplication**
- **Cancer cells do not self-destruct when they become worn out or damaged**
- **Cancer cells crowd out healthy cells**



Contact Inhibition

- **Normal Cells in culture exhibit contact inhibition**
- **Cancer cells lack contact inhibition feedback mechanisms. Clumps or foci develop**



Development of Cancer Cells

- **1st Mutation: alteration of DNA and reproduction of genetically altered cell**
- **2nd Mutation: further mutation, may have different appearance and more prone to division**
- **3rd Mutation: further mutation, speeds up the growth of the tumor**
- **4th Mutation: further mutation, causes the development of more aggressive cancer**

Induction of Cellular Proliferation

- **One category of proto-oncogenes and their oncogenic counterparts encodes proteins that induce cellular proliferation.**
- **Some of these proteins function as growth factors or growth factor receptors.**
- **In normal cells the expression of growth factors and their receptors is carefully regulated.**
- **Inappropriate expression of either a growth factor or its receptor can result in uncontrolled proliferation.**
- **Other oncogenes in this category encode products that function in signal transduction pathways or as transcription factors. Over-activity of any of these oncogenes may result in unregulated proliferation.**

Inhibition of Cellular Proliferation

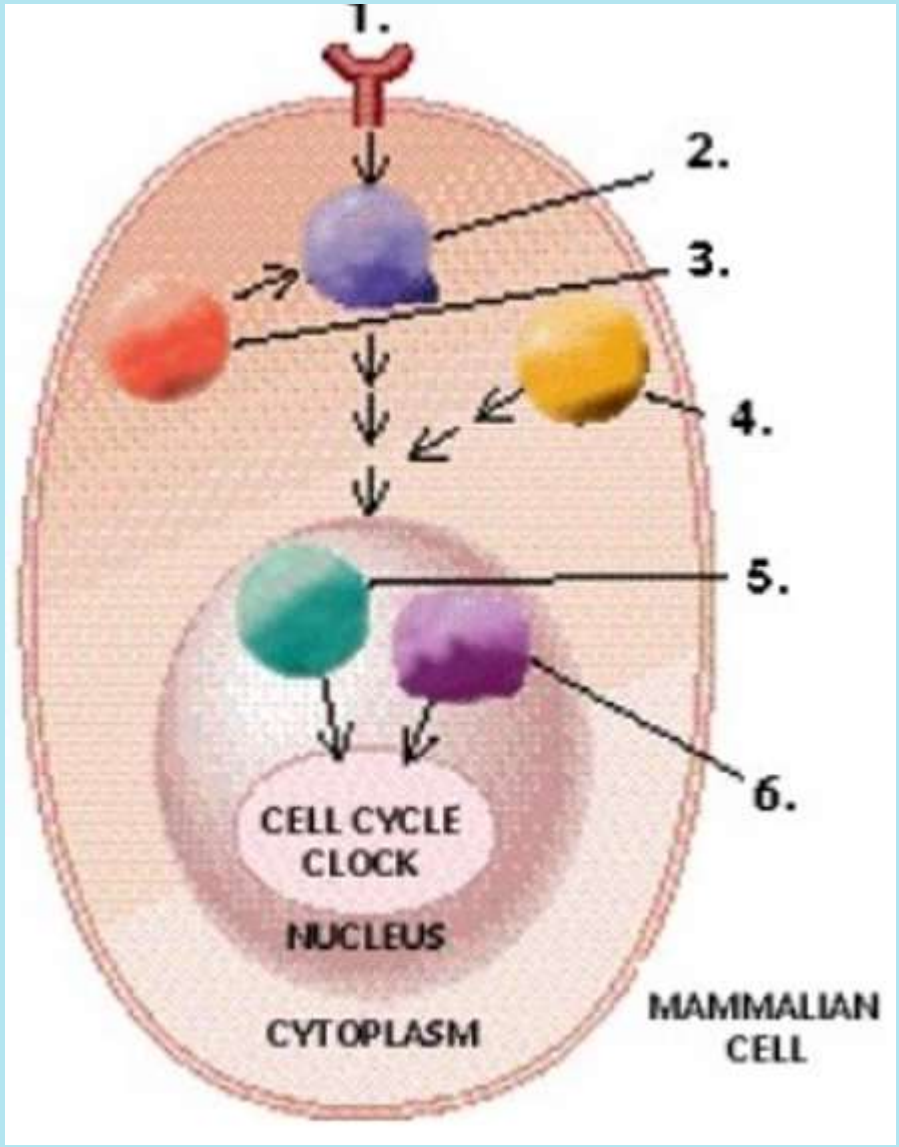
- **A second category of cancer associated genes called tumour suppressor genes or anti oncogenes.**
- **They encode proteins that inhibit excessive cell proliferation.**
- **Inactivation of these results in unregulated proliferation.**

Regulation of Programmed Cell Death

- **A third category of cancer associated genes regulates programmed cell death.**
- **These genes encode proteins that either block or induce apoptosis.**
- **Included in this category of oncogenes is bcl-2, an anti-apoptosis gene.**

Activation of Cell Division

1. **Growth Factor Receptor increased numbers in 20% of breast cancers**
2. **Ras Protein activated by mutations in 20-30% of cancers**
3. **Abl Kinase activated by abnormal chromosomes in chronic myelogenous leukaemia**
4. **Src Kinase activated by mutations in 2-5% of cancers**
5. **p53 Protein mutated or deleted in 50% of cancers**



Activation of Cell Division

- **Ras protein-Ras proteins function as binary molecular switches that control intracellular signaling networks. Ras-regulated signal pathways control such processes as actin cytoskeletal integrity, cell proliferation, cell differentiation, cell adhesion, apoptosis, and cell migration.**
- **Abl kinase-ABL is activated to stimulate cell proliferation or differentiation, survival or death, or migration.**
- **Src kinase-Src is a non-receptor protein tyrosine kinase that transduces signals that are involved in the control of a variety of cellular processes such as proliferation, differentiation, motility, and adhesion.**
- **p53 protein-p53, also known as TP53 or tumor protein is a gene that codes for a protein that regulates the cell cycle and hence functions as a tumor suppression. It is very important for cells in multicellular organisms to suppress cancer.**

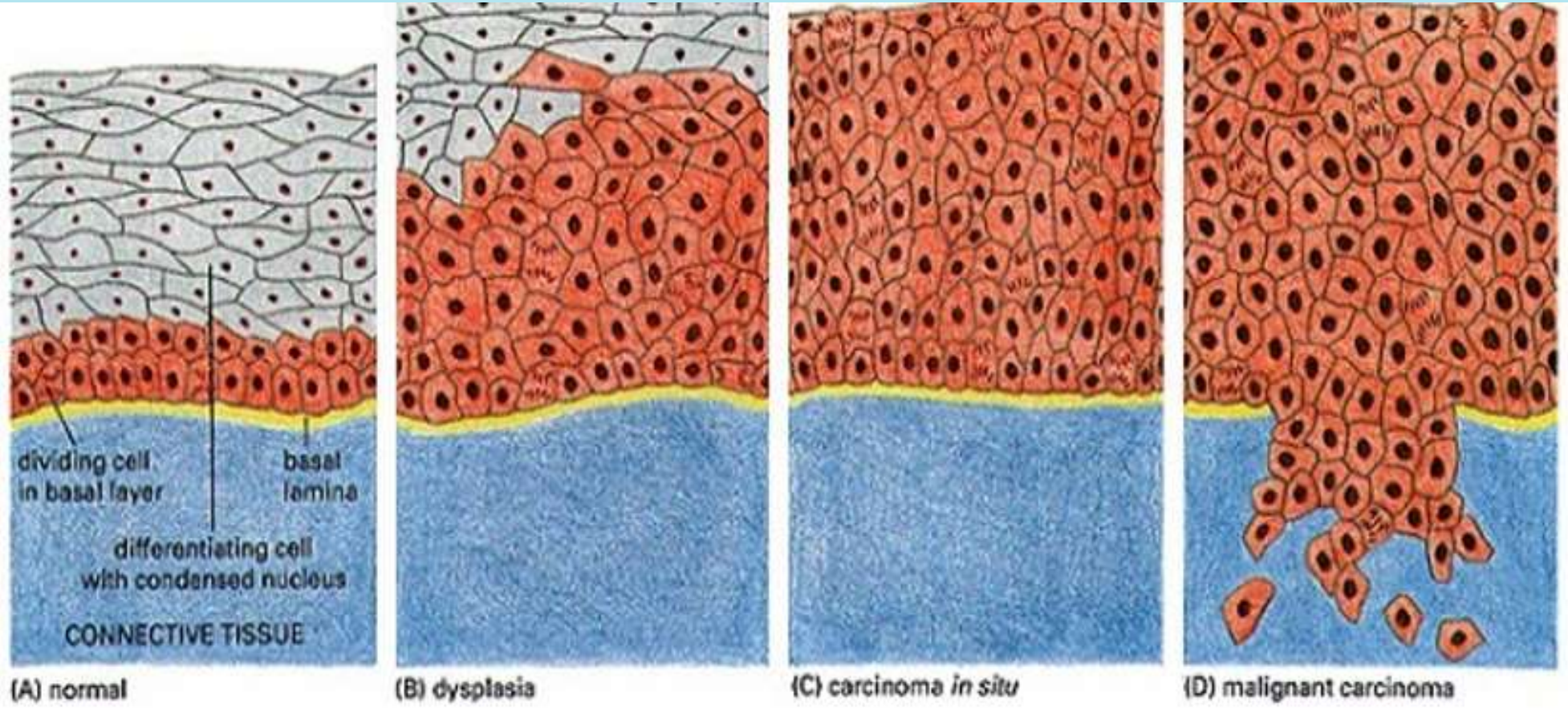
Benign or Malignant

- **Benign tumours do not spread from their site of origin, but can crowd out (squash) surrounding cells, e.g., brain tumour, warts**

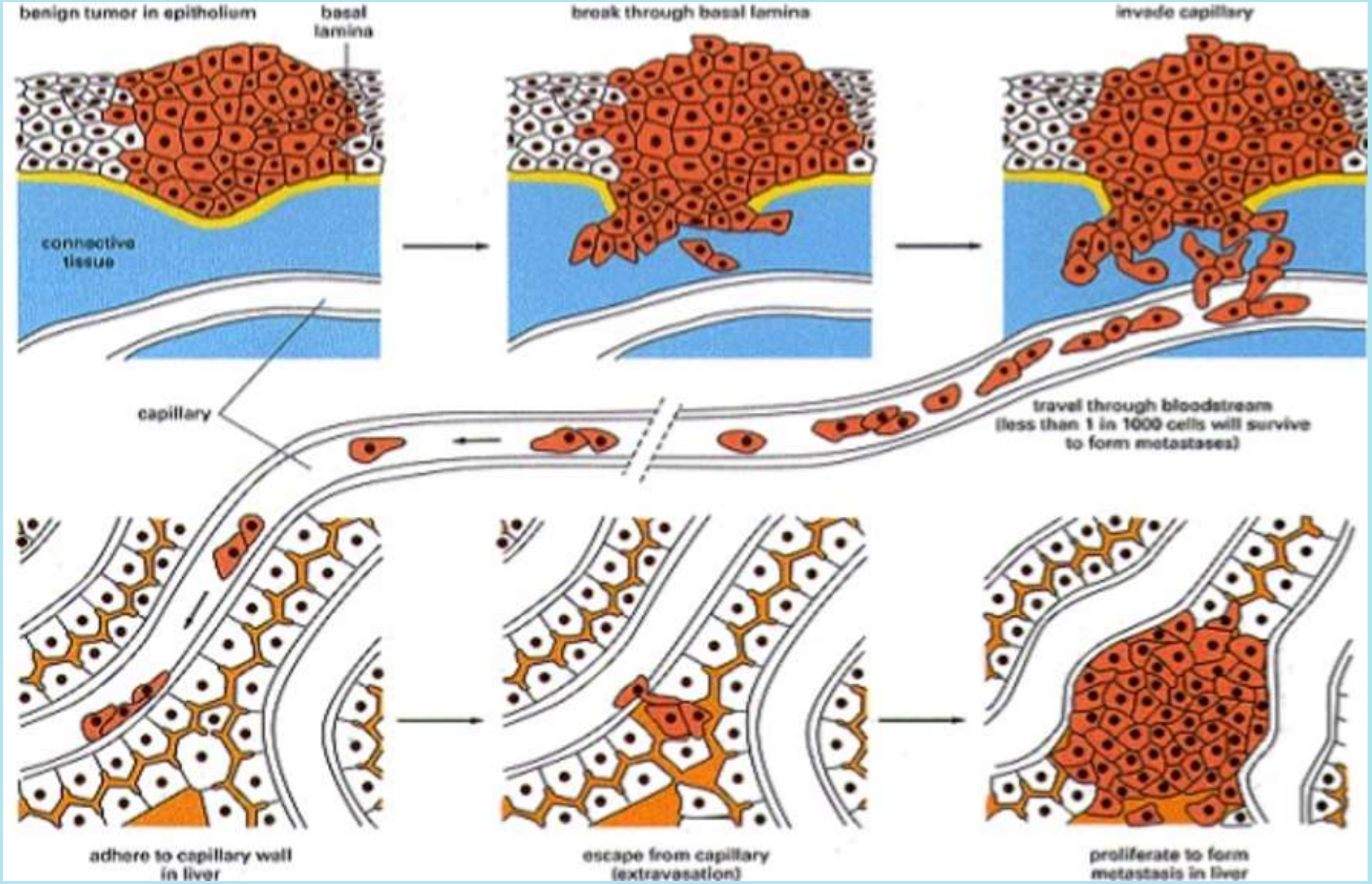
- **Malignant tumours can spread from the original site and cause secondary tumours. This is called metastasis. They interfere with neighbouring cells and can block blood vessels, the gut, glands, lungs etc.**

Metastasis – establishment of new tumour sites at other locations throughout the body.

Metastasis Carcinoma: derived from endoderm or ectoderm



Events in Metastasis



Mutations can be caused by ..

- **Carcinogens**
  - **Chemical – e.g., benzo(a)pyrene**
  - **Radiation – e.g., X rays**
  - **Viruses**

- **Hereditary predisposition**

Major Chemical Carcinogens

Direct Acting Carcinogens

Alkylating Agents

- Beta-propiolactone
- Dimethyle sulphate
- Diepoxybutane
- Anticancer drugs (cyclophosphamide, chlorambucil, nitro-soureas and others

Acylating Agents

- 1-Acetyle imidazole
- Dimethylecarbamyl chloride

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-Napthylamine (beta-napthylamine)
- Benzidine
- 2-Acetylaminofluorene
- Dimethylaminoazobenzene (butter yellow)

Natural Plant and Microbial Products

- Aflatoxin B1
- Griseofulvin
- Cycasin
- Safrole
- Betel nuts

Others

- Nitrosamine and amides
- Vinyl chloride, nickel, chromium
- Insecticides, fungicides
- Polychlorinated biphenyls

Direct Acting Carcinogens

- **Direct-acting agents require no metabolic conversion to become carcinogenic. have highly reactive electrophile groups that directly damage DNA, leading to mutations and eventually cancer.**

- **Examples are : cancer chemotherapeutic drugs (e.g., alkylating agents) e.g., leukaemia, lymphoma, Hodgkin lymphoma, and ovarian carcinoma, non-neoplastic disorders, such as rheumatoid arthritis or Wegener granulomatosis.**

- **May evoke later a second form of cancer, usually leukaemia.**

Indirect Acting Carcinogens

- **The designation indirect-acting agent refers to chemicals that require metabolic activation & conversion to an ultimate carcinogen before they become active**
- **Indirect-acting agents are not active until converted to an ultimate carcinogen by endogenous metabolic pathways e.g.. endogenous enzymes like cytochrome P-450 oxygenase.**
- **Examples: Benzopyrene, Polycyclichydrocarbons, aromatic amines and Azo dyes , Aflatoxin B1, insecticides, fungicides, nitrites used as food preservatives**

Mechanisms of Action of Chemical Carcinogens

- **Initiation**
- **Promotion**
- **The application of an initiator may cause the mutational activation of an oncogene such as RAS**
- **Subsequent application of promoters leads to clonal expansion of initiated (mutated) cells.**
- **Forced to proliferate, the initiated clone of cells accumulates additional mutations, developing eventually into a malignant tumour.**

Etiology of Cancer

- **Chemical carcinogens.**
- **Radiation carcinogenesis.**
- **Viral oncogenesis.**

Ionizing Radiation

- **Ionizing radiation includes: X-rays, gamma rays, as well as particulate radiation; alpha, beta, protons, neutrons and primary cosmic radiation. All forms are carcinogenic with special sensitivity in:**
  - **Bone Marrow: Acute leukemia occurs before other radiation-induced neoplasia (Seven year latent period in atomic bomb survivors).**
  - **Thyroid: Carcinoma occurs in 9 % of those exposed during infancy or childhood.**
  - **Lung: Increased frequency of lung cancer in miners exposed to Radon gas (an alpha particle emitter).**

Ionizing Radiation

- **The oncogenic properties of ionizing radiation are related to its mutagenic effects; it causes chromosome breakage, translocations, and, less frequently, point mutations.**
- **Double-stranded DNA breaks seem to be the most important form of DNA damage caused by radiation.**
- **There is also some evidence that non-lethal doses of radiation may induce genomic instability, favouring carcinogenesis**

Ultraviolet Light

- **Strong epidemiologic relationship to squamous cell ca, basal cell ca , and melanoma-in fair skinned people.**
- **Causes formation of pyrimidine dimmers in the DNA leading to mutations.**
- **This type of DNA damage is repaired by the nucleotide excision repair pathway. With extensive exposure to UV light, the repair systems may be overwhelmed, and skin cancer results**
- **Individuals with defects in the enzymes that mediate DNA excision-repair are especially susceptible.**

VIRUSES
DNA & RNA

RNA Tumour Viruses

Retrovirus	Associated Tumour
Rous sarcoma virus	Sarcoma (chickens)
Human T-cell leukaemia virus (HTLV-1)	Adult T-cell leukaemia/lymphoma (man)
Human immunodeficiency virus (HIV-1)	Kaposi's sarcoma (man)

- **Retrovirus: A virus that is composed not of DNA but of RNA. Retroviruses have an enzyme, called reverse transcriptase, that gives them the unique property of transcribing their RNA into DNA after entering a cell. The retroviral DNA can then integrate into the chromosomal DNA of the host cell, to be expressed there. Cytopathic retroviruses such as HIV-1 and HIV-2 induce changes in the host cell that lead to malignant transformation.**

- **In some cases retrovirus induced transformation is related to the presence of oncogenes or cancer genes carried by the retroviruses.**

- **One of the best studied transforming retroviruses is the Rous sarcoma virus.**

- **The human T-lymphotropic virus, human T-cell lymphotropic virus, or human T-cell leukemia-lymphoma virus (HTLV) family of viruses are a group of human retroviruses that are known to cause a type of cancer called adult T-cell leukemia/lymphoma and a demyelinating disease called HTLV-1 associated myelopathy/tropical**

DNA Oncogenic Viruses

DNA Viruses	Associated Human Cancer	Areas of High Incidence	Other Suspected Risk Factors
Epstein-Barr Virus (EBV)	Burkitt's lymphoma Nasopharyngeal carcinoma	Tropical Africa Southern China South East Asia Eskimos in Alaska and Greenland	Malaria Salted fish in infancy Histocompatibility genotype
Hepatitis B Virus (HBV)	Hepatocellular carcinoma (hepatoma)	South East Asia Tropical Africa	Aflatoxin from fungal contamination of food Alcoholism
Human Papilloma Virus (HPV) (subtypes 16 and 18)	Carcinoma of the uterine cervix	Worldwide	Smoking

- **The Epstein–Barr virus (EBV, sometimes abbreviated as EPV), formally called Human gammaherpesvirus 4, is one of the nine known human herpesvirus types in the herpes family, and is one of the most common viruses in humans. It causes the disease BURKITT LYMPHOMA.**

- **Burkitt lymphoma is a form of non-Hodgkin's lymphoma in which cancer starts in immune cells called B-cells. Recognized as a fast growing human tumor, Burkitt lymphoma is associated with impaired immunity and is rapidly fatal if left untreated.**

- **Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease. The virus is most commonly transmitted from mother to child during birth and delivery, as well as through contact with blood or other body fluids. It can cause hepatocellular carcinoma.**
- **Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Hepatocellular carcinoma occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection.**

- **Human papillomavirus (HPV) is a viral infection that's passed between people through skin-to-skin contact. There are over 100 varieties of HPV, more than 40 of which are passed through sexual contact and can affect your genitals, mouth, or throat.**

Types of Cancer

- **Carcinomas**
- **Sarcomas**
- **Lymphomas**
- **Leukaemias**

Lung Cancer

- **Killed 164,000 in year 2000**
- **Prevention researchers theorize: 90% of all lung cancers could be avoided by not smoking**

Types of Cancer

- **Carcinoma is a type of cancer that starts in cells that make up the skin or the tissue lining organs, such as the liver or kidneys. Like other types of cancer, carcinomas are abnormal cells that divide without control. They are able to spread to other parts of the body, but don't always.**

- **A sarcoma is a cancer that arises from transformed cells of mesenchymal (connective tissue) origin. Connective tissue is a broad term that includes bone, cartilage, fat, vascular, or hematopoietic tissues, and sarcomas can arise in any of these types of tissues.**

- **Lymphoma is cancer that begins in infection-fighting cells of the immune system, called lymphocytes. These cells are in the lymph nodes, spleen, thymus, bone marrow, and other parts of the body. When you have lymphoma, lymphocytes change and grow out of control.**

- **Leukaemia is a cancer of the blood or bone marrow. Bone marrow produces blood cells. Leukaemia can develop due to a problem with blood cell production. It usually affects the leukocytes, or white blood cells.**

Types of Cancer

Breast Cancer

- **One in eight women**
- **Risk increases with age**
- **Risk factors supported by research**
- **Prevention – self-exam and mammography**
- **Treatment**

Types of Cancer

Colon and Rectum Cancer

- **3rd most common in men and w omen**
- **135, 400 in 2001 were diagnosed**
- **Warning signals - blood in the stool, rectal bleeding**

Prostate Cancer

- **Most common in males today**
- **189,000 new cases were diagnosed in 2002**
- **Estimated 30,200 men will die**

Types of Cancer

Skin Cancer

- **1.3 million cases of skin cancer**
- **Treatable – basal or squamous**
- **Virulent – malignant melanoma**
- **ABCD rule about melanoma**

Types of Cancer

Testicular Cancer

- **Age 17-34 at greatest risk**
- **Cause is unknown**
- **Undescended testicles present a great risk**

Types of Cancer

Ovarian Cancer

- **4th leading cause of death in young women**
- **Enlargement of abdomen is a common sign**
- **Prevention - annual pelvic exam**

Endometrium (Uterine) Cancer

- **Pap test for early detection**
- **Risk – early onset of intercourse**
- **Warning – abnormal bleeding**

Types of Cancer

Cancer of the Pancreas

- **‘Silent’ disease**
- **29,700 cases in 2002**
- **Only 4% survive**
- **Contributors - inflammation, diabetes, high-fat diet**

Types of Cancer

Leukaemia

- **Cancer of blood forming tissues**
- **Leads to creation of immature white blood cells**
- **Symptoms - fatigue, paleness, weight loss**
- **Can be acute or chronic**

Treatment of Cancer

Treatment options depend on the type of cancer, its stage (if the cancer has spread) and general health. The goal of treatment is to kill as many cancerous cells while minimizing damage to normal cells nearby.

The four main treatments are

1. **Surgery – directly removing the tumour**
2. **Chemotherapy – using chemicals to kill cancer cells**
3. **Radiation – using X rays to kill cancer cells**
4. **Immunotherapy – boosting immune system**

Cancer Immunotherapy

- **Biological therapy or biotherapy**
- **Immunotherapy for cancer was first introduced by Rosenberg et. al, National Institute of Health, USA**
- **It is a type of cancer treatment designed to boost body's natural defences to fight cancer**
- **It harnesses and enhances the innate power of the immune system**
- **It represents the most promising cancer treatment approach since the development of first chemotherapy in late 1940s**
- **Cancer immunotherapy today is highly active & exciting field, with unprecedented potential to deliver on the decade-long promise of discovering, developing, delivering safe and effective treatments that make a meaningful difference in the lives of patients fighting the disease**

Why Immune System

- **Our immune system is a collection of organs, special cells, and substances that help protect us from infections and some other diseases.**
- **Immune cells and the substances travel through out our body to protect us from germs that cause infections.**
- **Germs like viruses, bacteria, and parasites are like hostile, foreign armies that are not normally found in your body.**
- **They try to invade your body to use host resources and result in harmful effects.**
- **Our immune system is our body's defence force.**
- **Sometimes the immune system doesn't see the cancer cells as foreign because the cells are not different enough from normal cells. Sometimes the immune system recognizes the cancer cells, but the response might not be strong enough to destroy the cancer.**
- **To overcome this, researchers have found ways to help the immune system recognize cancer cells and strengthen its response, so that immune system will destroy them.**

Why Immune System

- **Immunotherapy use immune system components such as proteins called antibodies that are made in the lab.**
- **They boost the immune system once they are in the body.**
- **The antibodies themselves target certain proteins that help cancer cells grow.**
- **By binding to cancer-aiding proteins, the antibodies stop cancer cells from growing or make them die.**
- **These types of antibodies are also known as TARGETED THERAPHY.**

Types of Immunotherapy

- **MONOCLONAL ANTIBODIES: These are INVITRO versions of immune system proteins. Antibodies can be very useful in treating cancer because they can be designed to attack a very specific part of a cancer cell.**

- **CANCER VACCINES: Vaccines are substances put into the body to start an immune response against certain diseases. We usually think of them as being given to healthy people to help prevent infections. But some vaccines can help prevent or treat cancer.**

- **NON-SPECIFIC IMMUNTHERAPIES: These treatments boost the immune system in a general way, but this can still help the immune system attack cancer cells.**

Monoclonal Antibodies

- **One way the immune system attacks foreign substances in the body is by making large numbers of antibodies.**
- **An antibody is a protein that sticks to a specific protein called an antigen**
- **Antibodies circulate in the body until they find and attach to the antigen.**
- **Once attached, they can recruit other parts of the immune system to destroy the cells containing the antigen.**
- **The copies of that antibody synthesised in the lab. These are known as monoclonal antibodies (mAbs or moAbs).**

Monoclonal Antibodies

- **To make a monoclonal antibody, researchers first have to identify the right antigen to attack. For cancer, this is not always easy.**

- **Over the past couple of decades, the US Food and Drug Administration (FDA) has approved more than a dozen mAbs to treat certain cancers.**

Naked monoclonal antibodies

- **Example : alemtuzumab (Campath), which is used to treat some patients with chronic lymphocytic leukaemia (CLL).**
- **Alemtuzumab binds to the CD52 antigen, which is found on cells called lymphocytes (which include the leukaemia cells).**
- **Once attached, the antibody attracts immune cells to destroy these cells.**

Cancer Vaccines

- **Vaccines use weakened or killed germs like viruses or bacteria to start an immune response in the body. Getting the immune system ready to defend against these germs helps keep people from getting infections.**

- **Some cancer treatment vaccines are made up of cancer cells, parts of cells, or pure antigens. Sometimes a patient's own immune cells are removed and exposed to these substances in the lab to create the vaccine. Once the vaccine is ready, it's injected into the body to increase the immune response against cancer cells.**

- **Cancer vaccines cause the immune system to attack cells with one or more specific antigens. Because the immune system has special cells for memory, it's hoped that the vaccine might continue to work long after it's given.**

- **Sipuleucel-T (Provenge®) is the only vaccine approved so far by the US Food and Drug Administration (FDA) to treat cancer. It is used to treat advanced prostate cancer that is no longer treat advanced prostate cancer that is no longer being helped by hormone therapy.**

Non Specific Cancer Immunotherapies and Adjuvant

- **Non-specific immunotherapies don't target cancer cells specifically.**

Cytokines

- **Cytokines are chemicals made by some immune system cells. They are crucial in controlling the growth and activity of other immune system cells and blood cells in the body.**
- **Cytokines are injected, either under the skin, into a muscle, or into a vein. The most common ones are discussed here.**

Interleukins

- **(IL-2) helps immune system cells grow and divide more quickly. A man-made version of IL-2 is approved to treat advanced kidney cancer and metastatic melanoma.**

Interferons

- **Interferons, first discovered in the late 1950s, help the body resist virus infections and cancers. The types of interferon (IFN) are named after the first 3 letters of the Greek alphabet: IFN-alfa, IFN-beta, and IFN-gamma.**
- **Only IFN-alfa is used to treat cancer. It boosts the ability of certain immune cells to attack cancer cells. It may also slow the growth of cancer cells directly, as well as the blood vessels that tumours need to grow.**