Pathways of Spread

Malignant tumours are spread by one of two pathways:

1. Lymph vessels (lymphatic spread) which is more typical of **carcinomas**.

2. Blood vessels (haematogenous spread) which is favoured by **sarcomas**.

Lymphatic Spread

- The tumour cells lodge first in the **initial lymph node** that receives drainage from the tumour site **(sentinel node).**
- Once in this lymph node, the cells may **die** because of the lack of a proper environment, **remain dormant** for unknown reasons, or **grow into a discernible mass**.
- If they survive and grow, the cancer cells may spread from more distant lymph nodes to the **thoracic duct**, and then gain access to the **blood vessles**.
- E.g. **Breast cancer** is almost lymphatic spread.

Haematogenous spread

- Cancer cells commonly invade **capillaries and venules**, whereas thicker-walled arterioles and arteries are relatively resistant but arterial spread may occur.

- The **liver** and **lungs** are the most frequent metastatic sites for haematogenous spread. Since venous blood from the gastrointestinal tract, pancreas, and spleen is routed through the **portal vein to the liver and all vena cava blood flows to the lungs.**

Angiogenesis

Cancer cells and other cells in the microenvironment such as inflammatory cells (e.g., macrophages) or other stromal cells associated with the tumours secrete angiogenesis factors such as **vascular endothelial growth factor (VEGF)** that enable the development of new blood vessels within the tumour.

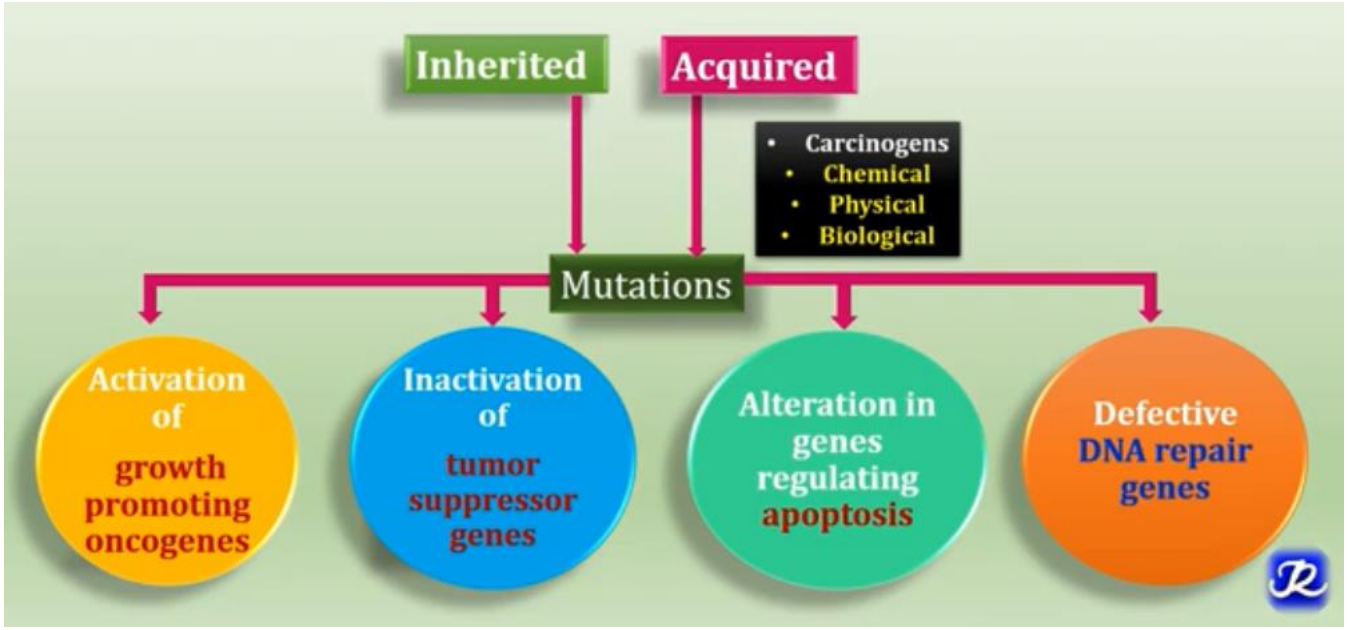
In normal cells, the p53 gene can stimulate expression of antiangiogenic molecules, such as **thrombospondin-1**, and repress expression of proangiogenic molecules, such as VEGF. Thus, loss of p53 activity in cancer cells promotes angiogenesis.

Etiology of cancer

The cause or causes of cancer can be viewed from two perspectives:

(1) The genetic and molecular mechanisms.

(2) The external factors such as age, heredity, and environmental agents.

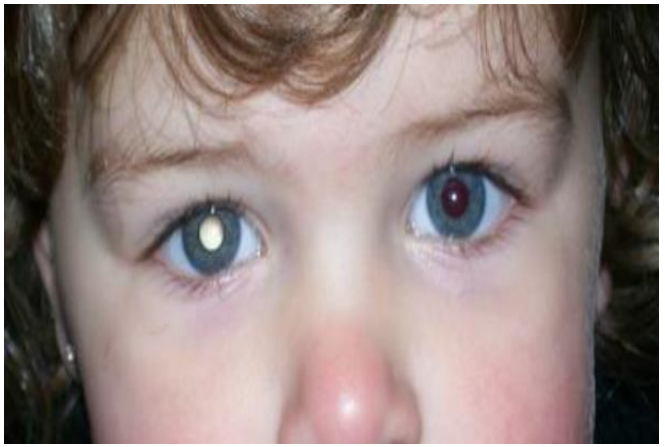


Etiology of cancer

Cancer caused by gene alterations that may result from exposure to several factors such as:

- ✓ **Age.**
- ✓ **Heredity.**
- ✓ **Obesity and Hormone.**
- ✓ **Viral and microbial Agents.**
- ✓ **Chemical agents such as cigarette smoke.**
- ✓ **Physical agents such as ionizing and Ultraviolet radiations.**

Heredity



Several cancers exhibit an **autosomal dominant inheritance pattern** that greatly increases the risk of developing a tumour.

E.g. **Retinoblastoma (RB)** approximately **40%** of retinoblastomas are inherited. Carriers of the **mutant RB suppressor gene** have a **10,000-fold** increased risk of developing retinoblastoma.

Heredity

Persons who inherit the mutant gene are born with **one normal and one mutant copy of the gene**. In order for cancer to develop, the normal gene must be inactivated, usually through a somatic mutation.

Breast cancer, for example, occurs more frequently in women whose grandmothers, mothers, aunts, and sisters also have experienced a breast malignancy.

Two tumour suppressor genes, called **BRCA-1 and BRCA-2** have been implicated in a genetic susceptibility to breast cancer. These genes have also been associated with an increased risk of **ovarian, prostate, pancreatic, colon**, and other cancers.

Obesity and Hormone

- Obesity has been associated with increased levels of sex hormones (androgens and estrogens), which can act as mitogens that stimulate cell proliferation, inhibit apoptosis, and therefore increase the chance of malignant cell transformation.
- The production of **estrogens** by the ovary stimulates **breast cancer** while the production of **androgen** stimulates **prostate cancer**.
- Because of the evidence that endogenous hormones affect the risk of these cancers, concern exists regarding the effects on cancer risk if the same or closely related hormones are administered for therapeutic purposes.

Viral and Microbial Agents

1. There is also an association between infection with the bacterium **Helicobacter pylori** and gastric adenocarcinoma and gastric lymphomas.

Several RNA and DNA viruses can induce cancer

2. RNA viruses(retrovirus): human T-cell leukaemia virus-1 (HTLV-1) is the only known retrovirus to cause cancer in humans.

3. DNA viruses: only four DNA viruses have been implicated in human cancers: the **human papilloma virus (HPV), Epstein-Barr virus (EBV)** cause Burkitt lymphoma and nasopharyngeal cancer**, hepatitis B virus (HBV), and human herpesvirus 8 (HHV-8)**.

Manifestations of cancer

1. Anorexia and cachexia: Many cancers are associated with weight loss and wasting of body fat and muscle tissue, accompanied by profound weakness and anorexia. Cancer cell causes anorexia by **suppressing satiety centres** in the hypothalamus and **increasing the synthesis of lipoprotein lipase,** an enzyme that facilitates the release of fatty acids from lipoproteins so that they can be used by tissues

2. Anaemia: It occurs due to blood loss, haemolysis, impaired red cell production, or treatment effects. Drugs used in treatment of cancer are cytotoxic and can decrease red blood cell production. Erythrocyte production can be impaired due to nutritional efficiencies and bone marrow failure.

3. Fatigue and sleep disorders: The cause of cancer-related fatigue is largely unknown but is probably multifactorial and involves the dysregulation of several interrelated physiologic, biochemical, and psychological systems.

4. Pain: In its late stages, cancer often causes pain.

5. Paraneoplastic syndromes are a group of conditions developing in patients with advanced cancer. Cancer can produce manifestations in sites that are not directly affected by the disease. **E.g. Small cell lung cancer produces ADH.**

The grading and staging of malignant tumours

The two basic methods for classifying tumour are:

1. Grading according to the histologic or cellular characteristics of the tumour.

2. Staging according to the clinical spread of the disease. It is useful in determining the choice of treatment for individual patients, estimating prognosis, and comparing the results of different treatment regimens.

Both methods are used to determine the course of the disease and aid in selecting an appropriate treatment or management plan.

The grading of tumours

The grading of tumours involves the microscopic examination of tumour cells to determine their level of differentiation. It is based on the **degree of differentiation.**

Accordingly, on a scale ranging from **grade I to IV.** **Grade I** neoplasms are **well differentiated** and **Grade IV** are **poorly differentiated** and **display marked anaplasia.**

Anaplasia is a change in the structure of cells and in their orientation to each other that is characterized by a loss of cell differentiation.

The staging of tumours

The staging of cancers uses radiographic examination (CT and MRI) and, in some cases, surgical exploration to determine **the size of the primary tumour, its extent of local growth, lymph node involvement, and presence of distant metastasis.**

The TNM staging system was developed by the Union Internationale Cancer Centre (UICC), and the American Joint Committee (AJC) system. In the **TNM** system:

T1, T2, T3, and T4 describe the increasing size of the primary tumour.

N0, N1, N2, and N3 advancing node involvement.

M0 or M1, describe the absence or presence of distant metastasis.

Diagnostic Methods

The diagnosis of cancer including:

1. Blood tests for tumour markers: Some cancers may produce antigens, these antigens may be clinically useful as markers to indicate the presence, recurrence, or progressive growth of cancer.

2. Cytological studies and tissue biopsy.

3. Ultrasound and x-ray studies.

4. Magnetic resonance imaging (MRI)

5. Computed tomography (CT).

Cancer treatment

Cancer treatment including:

1. Surgery.
2. Radiation.
3. Chemotherapy.
4. Hormonal therapy.
5. Biotherapy (immunotherapy).