

# Unit 13

## CANCER |

### Structure

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13.1	Introduction	Alpha-fetoprotein
	Expected Learning Outcomes	Carcinoembryonic Antigen
13.2	Morphological and Metabolic Changes in Tumor Cells	13.4 Carcinogens
	Morphological Changes	Classification of Carcinogens
	Clinical Importan	13.5 Diagnosis of Cancer
	Metabolic Changes in Tumor Cells	13.6 Summary
13.3	Tumor Markers	13.7 Terminal Questions
		13.8 Answers

### 13.1 INTRODUCTION

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Cancer is a complex disease that is characterized by uncontrolled growth of cells by throwing off the balance between cell growth and cell death. Many genetic and environmental factors play role in its initiation and development. It is a disease of global concern because of number of deaths caused by cancer. Therefore, it is important to understand the type of changes that convert normal cell to cancer as well as to identify the biomarkers that can be used to detect cancer and its progression. Early the detection, better the chances of recovery.

In this unit we shall discuss about the clinical aspects of cancer. Morphological and metabolic changes occurring in tumor cells will be explained. Different types of tumor markers and their significance will also be discussed. The agents that cause cancers are called carcinogens, their nature and mechanism of action will also be described.

## Expected Learning Outcomes

After studying this unit, you should be able to:

- ❖ learn about the morphological and metabolic changes in tumor cells;
- ❖ give examples of tumor markers and explain their role in diagnosis of tumors; and
- ❖ define carcinogens and discuss their role in cancer development.

## 13.2 MORPHOLOGICAL AND METABOLIC CHANGES IN TUMOR CELLS

Cancer is a multi-step process in which cells undergo metabolic and behavioral changes, leading them to proliferate in an excessive and untimely way. Before we go further, let us understand what is difference between tumor and cancer. Tumor is any abnormal growth of cells and is of two types: benign (non-cancerous) or malignant (cancerous). So, tumors do not spread to other organs and are generally harmless. However, they may pose problems if they grow to abnormally large size and start compressing nearby organs. Cancers are the tumors that can invade and spread to other parts of the body; this property is known as metastasis. Thus, we can say all cancers are tumors, but not all tumors are cancers.

Depending on the type of tissue affected, cancers are broadly classified into four types:

Tumor pathogenesis refers to the study of mechanisms that control normal cells and tissues and the molecular changes that take place in the cancerous condition, leading to the initiation, maintenance, and metastasis of tumors.

**Carcinomas:** These are the most common type of cancer, originating in epithelial cells that line the surfaces of organs and glands. Examples include lung, breast, colon, and prostate cancers.

**Sarcomas:** Cancers that develop in connective tissues like bone, cartilage, muscle, blood vessels, and fat.

**Leukemias:** Cancers of the blood-forming tissue, such as bone marrow, leading to an overproduction of abnormal white blood cells.

**Lymphomas:** These cancers originate in the lymphatic system, which is part of the immune system, and include Hodgkin and non-Hodgkin lymphomas.

Cancer is caused due to inherited genetic changes that modify the DNA sequence. Another way is to change the programme of cells is to modify the conformation of chromatin, the structure that wraps up DNA and regulates its access by DNA reading, copying and repair machineries. Such changes are called “epigenetic”. Other causes may be exposure to carcinogens like radiation, certain chemicals; unhealthy life style such as smoking or infections such as hepatitis B or C leads to liver cancer, Human papilloma virus (HPV) causes cervical cancer. Some of the characteristics of cancerous cells that differentiate them from normal cells are; uncontrolled growth, invasion to other organs, loss of contact inhibition, evasion of apoptosis, capacity to escape the immune system, loss of differentiation, changes in cell surface, increased

mobility etc. In order to support the uncontrolled growth, cancer cells undergo alterations in their morphology and metabolic pathways. We shall discuss about these changes in this section.

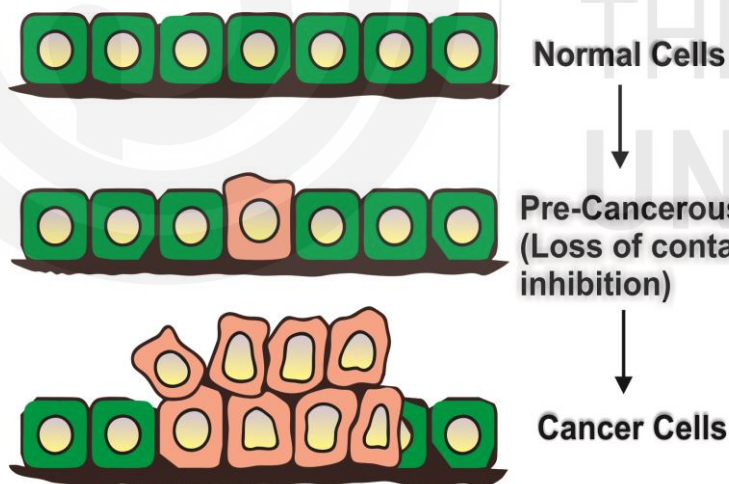
### 13.2.1 Morphological Changes

Morphological changes are noted at the level of cell shape, size, surface as well as internal structural level. Let's us understand the major morphological changes seen in the cancer cells.

**Nuclear Changes:** These include enlarged nucleus with irregular shape compared to the smooth, oval shape of normal cells. The nucleoli, also become more prominent or enlarged. Changes are seen in the chromosome number, structure, and organization. Increased staining intensity of the nucleus (hyperchromasia) can be observed due to increased DNA content.

**Cytoplasmic Changes:** Cancer cells may have a smaller amount of cytoplasm compared to normal cells. It appears paler or more intensely stained than normal cells.

**Cell Shape and Adhesion:** Cancer cells exhibit various irregular shapes, deviating from the typical round or oval shape of normal cells. These lose the property of contact inhibition; therefore, they keep on dividing even after coming in contact with another cell. Reduced adhesiveness to neighboring cells and the extracellular matrix, can contribute to their ability to invade and metastasize, resulting in a chaotic cell population (Fig 13.1).



Do you know that normal cells will divide until they are in contact with the neighboring cells. At this point they stop growing. Thus, contact inhibition results in a sheet of cells just one layer thick, referred to as a monolayer. Cancer cells typically lose contact inhibition, causing them to pile up and form tumors.

Fig 13.1: Loss of contact inhibition results in chaotic growth of cancer cells.

**Organelle Changes:** Cancer cells may exhibit changes in the size, shape, or number of cellular organelles like the endoplasmic reticulum, mitochondria, and Golgi apparatus. The cytoskeleton, which provides structure and support to the cell, can be altered in cancer cells, affecting cell shape, motility, and adhesion. structures. For example, the size of the endoplasmic reticulum and mitochondria often decreases, the Golgi apparatus is underdeveloped, and the number of peroxisomes increase (Fig. 13.2).

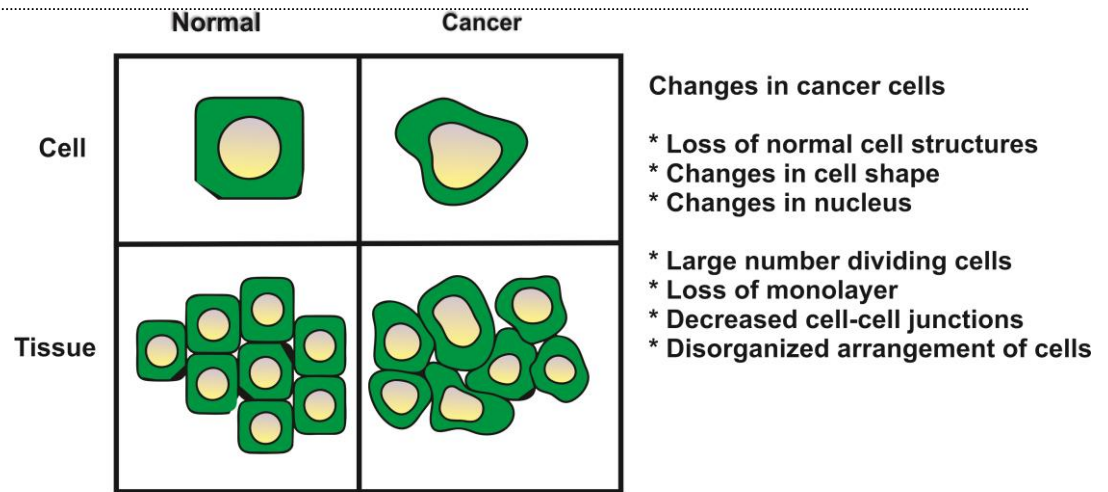


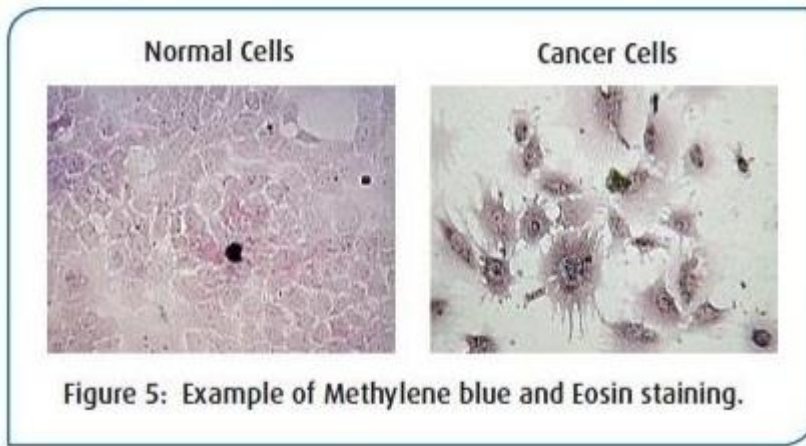
Fig. 13.2: Difference in the morphology of normal and cancer cells.

**Cell surface changes:** Changes in the cell membrane affect the way it responds to various signalling pathways. Proteins and carbohydrates present in the cell membrane that act as enzymes and as cell surface receptors can also undergo changes. There may be increase or diminution in the number of surface receptors, changing cell sensitivity to the regulating mechanisms of the host. The structural changes of proteins or surface receptors may appear so that these no longer react with the corresponding ligand or new surface molecules appear such as characteristic of the embryonic tissue, which are hidden at the surface of adult cells. Abnormal surface molecules are able to act as antigens, thereby altering the recognition by the mechanisms of humoral and cellular defences.

### 13.2.2 Clinical Importance

Cancer is a major cause of death globally. Therefore, understanding and detecting the morphological changes of cancer cells is a key component of cancer diagnosis, with histologists and pathologists routinely using these characteristics to identify and classify tumors. These morphological features help clinicians to stage and grade tumors, which helps determine the extent of cancer spread and aggressiveness. These changes reflect the underlying biological processes of cancer development, including uncontrolled cell growth, invasion, and metastasis. Further, alteration in the cell function and gene expression have been observed that could lead to new therapeutic targets for cancer treatment.

For diagnosis, the suspected cancerous tissue is biopsied and fixed by a chemical or physical procedure to preserve the cells. The fixed tissue is then hardened, cut into very thin sections (one-cell thick), and placed onto a microscope slide. Finally, the prepared sections are treated using a variety of dyes that specifically stain the cellular structures. Methylene blue and eosin are two common dyes used to identify specific cellular features: methylene blue stains the nuclear material a deep blue color, while eosin will stain the cytoplasm and connective tissue a lighter pink (Fig. 13.3). Together, these dyes allow a histologist to quickly and easily observe changes in cell structure and composition.



**Fig. 13.3: Visual differences between normal and cancer cells when stained with Methylene blue and Eosin. Normal cells appear more uniform in size and shape, forming a more organized and densely packed layer, exhibiting contact inhibition. Cancer cells show a loss of contact inhibition, leading to disorganized growth, irregular shapes and sizes, and often forming clumps or aggregates.**

### 13.2.3 Metabolic Changes in Tumor Cells

In addition to the morphological changes, cells undergo metabolic reprogramming. Oncogenes and tumor suppressor genes rewire cellular metabolism to meet the demands of rapid cell division, resist cell death, and adapt to hypoxic conditions within the tumor microenvironment (TME). Metabolites derived from these pathways serve as metabolic biomarkers that can provide valuable information about cancer metabolism and aid in diagnosis, prognosis, and develop targeted therapies aimed at disrupting cancer metabolism.

One critical aspect of metabolic reprogramming in cancer is the Warburg effect. It is one of the well-characterized metabolic alterations of cancer cells. Warburg observed that cancer cells prefer to use glucose by glycolysis for energy production even in the presence of adequate oxygen. **The preference of cancer cells for glycolysis over oxidative phosphorylation, despite its lower efficiency in ATP production, is a hallmark of many types of cancer and is known as the Warburg effect.** However, cancer cells compensate for this inefficiency by upregulating glucose transporters and glycolytic enzymes, leading to an increased glycolytic flux. This metabolic reprogramming supports rapid cell proliferation by providing both ATP and metabolic intermediates for biosynthetic processes, such as nucleotide and lipid synthesis. Despite the Warburg effect suggesting a reduced dependence on oxidative phosphorylation, many cancer cells still utilize mitochondrial respiration to meet energy demands and support biosynthetic pathways, playing crucial roles in apoptosis regulation and reactive oxygen species (ROS) production.

Other than glycolysis, glutaminolysis is highly increased that highlights the dependence of cancer cells on the amino acid glutamine. It serves as a key nitrogen donor for nucleotide and amino acid biosynthesis and replenishes tricarboxylic acid (TCA) cycle intermediates. Other amino acids like serine and glycine are also critical, with the serine-glycine-one-carbon (SGOC)

The tumor microenvironment (TME) refers to the complex ecosystem surrounding a tumor, comprised of non-cancerous cells such as immune cells, fibroblasts, endothelial cells; blood vessels; the extracellular matrix and various molecules. It plays an active role in tumor growth, progression, and response to therapy.

metabolism pathway supporting nucleotide synthesis and redox balance. Enzymes such as serine hydroxymethyltransferase (SHMT) and glycine decarboxylase (GLDC) are often upregulated, indicating their importance in cancer metabolism

Alterations in lipid metabolism include enhanced *de novo* lipogenesis and changes in fatty acid oxidation that provide essential components for membrane biogenesis and additional energy sources.

## 13.3 TUMOR MARKERS

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Tumor markers may be defined as quantifiable molecules, including DNA, RNA, proteins and metabolites, that are found in body fluids or tissues at an abnormal level that signal a pathologic condition, such as cancer. A biomarker might be a molecule secreted by a malignancy, or it can be a specific response of the body to the presence of cancer. Alterations in gene sequence or expression and in protein structure and function have been associated with every type of cancer and with their progression through the various stages of development. Changes in gene expression and in protein expression or modification can be used to detect cancer, determine prognosis and monitor disease progression and therapeutic response.

We just discussed about many metabolic pathways and metabolites that are increased in cancer cells. Many of enzymes of these pathways have been used as tumor markers for detection of certain cancers or used as drugs to treat the cancer cells.

These tumor markers may be found in body fluids, such as blood or urine. Other tumor markers are found in samples of cells that are removed from a tumor during a biopsy. Not all cancers have known tumor markers, and the tumor markers that are known don't always provide accurate information. That's because sometimes conditions other than cancer may also cause high levels of certain tumor markers. Presence of a tumor marker can't tell whether it is coming from cancer or some other another condition. Moreover, high levels of the tumor markers commonly found in certain type of cancer may not be present in some people. Therefore, measurements of tumor markers are usually combined with the results of other tests, such as biopsies or imaging, to diagnose cancer.

### 13.3.1 Alpha Fetoproteins

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$\alpha$ -fetoproteins (AFP) are important for fetal growth and are produced by fetal liver and yolk sac. Its levels are at peak during 13-15<sup>th</sup> week in mother's blood, while it peaks in amniotic fluid around 14<sup>th</sup> week. Abnormal levels of AFP during pregnancy indicated health issues with fetal growth and development, therefore, it is part of prenatal screening tests for birth defects. Abnormal levels of AFP may indicate risk of development of following diseases in child:

A neural tube defect, a serious condition in which a baby's brain, spine and/or spinal cord do not form properly.

Down syndrome, a genetic disorder that is associated with both mental and physical health challenges. These problems may range from mild to severe.

Edwards syndrome (trisomy 18), an uncommon genetic condition that causes an abnormal head shape and many organ defects. Most babies with this condition die in the first year of life.

Expression of these proteins reduces appreciably in adults. However, in certain cancers such as liver cancer or germ cell cancers, these are detected in large amount in adult blood making them a suitable marker for these cancers.

### 13.3.2 Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA) is a glycoprotein present in fetus in larger amount and is almost negligible in adults. Its levels are generally 2.5-3.0 ng/ml in non-smokers and slightly higher in smokers (5.0 ng/ml). Higher levels may indicate cancer; CEA level greater than 10 ng/ml suggests extensive disease while levels above 20 ng/ml may indicate that cancer is spreading. It is a tumor marker for colorectal, lung, breast, and pancreatic cancers. However, this test alone cannot be used as CEA is elevated in many non-cancerous conditions also such as liver problems, inflammatory bowel disease, lung infections, and other inflammatory conditions.

Tumor markers have been used to know the type and stage of the cancer and to get an estimate of prognosis. These are also used to study the effectiveness of a treatment and recurrence of cancer (Table 13.1).

**Table 13.1: List of the common tumor markers and their diagnostic use.**

Tumor antigen	Target Cancer	Sample used	Use
CA (cancer antigen)- 125	Ovarian Cancer	Blood	To help in diagnosis, assessment of response to treatment, and evaluation of recurrence
PSA (prostate-specific antigen)	Prostate cancer	Blood	To help in diagnosis, to assess response to treatment, and to look for recurrence
CEA (carcinoembryonic antigen)	Colon and rectum (colorectal or bowel cancer), Prostate, Ovary, Lung, Thyroid, Liver, Pancreas, Breast cancers	Blood	To check effect of treatment and detect recurrence

AFP (alpha-fetoprotein)	Liver, ovarian and testicular cancer	Blood	To help diagnose these cancers and follow response to treatment; to assess stage, prognosis (predict chances for recovery), and response to treatment of germ cell tumors
B2M (Beta 2 Microglobulin)	Multiple myeloma, Chronic lymphocytic leukemia (CLL), Certain types of lymphoma	Blood, urine, or cerebrospinal fluid (rare cases)	To determine prognosis and follow response to treatment; predict chances for recovery
Beta-human chorionic gonadotropin (Beta-hCG)	Choriocarcinoma and germ cell tumors	Urine or blood	To assess stage, prognosis, and response to treatment
BRCA1 and BRCA2 gene mutations	Breast, ovarian, pancreatic, and prostate cancers	Blood and/or tumor	To help determine treatment
Calcitonin	Medullary thyroid cancer	Blood	To aid in diagnosis, check whether treatment is working, and assess recurrence
CD20	Non-Hodgkin lymphoma	Blood	To help determine treatment
Chromosome 17p deletion	Chronic lymphocytic leukemia	Blood	To help in diagnosis and to determine treatment
EGFR	Non-small cell lung cancer and colorectal cancer	Tumor biopsy	To help determine treatment and prognosis
ROS1 gene rearrangement	Non-small cell lung cancer	Tumor	To help determine treatment

Source: [https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-](https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-)

list#:~:text=A%20tumor%20marker%20is%20anything,it%20is%20responding%20to%20treatment.

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## SAQ 1

Name the cancer/s for which following tumor markers are tested:

- a) AFP
  - b) CEA
  - c) EGFR
  - d) BRAC gene mutations
  - e)  $\beta$ -hCG
  - f) PSA
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## 13.4 CARCINOGENS

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Carcinogens are substances that can induce or increase the risk of developing cancer. Inhalation, ingestion, application or injection of these carcinogens induce malignant tumours or increase their incidence or shorten the time of tumour occurrence.

### 13.4.1 Classification of Carcinogens

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Carcinogens fall into three broad categories; physical, chemical and biological.

**Chemical Carcinogens:** Chemical carcinogens can be categorized in many ways. One of the ways of categorizing carcinogen is whether it is **genotoxic or non-genotoxic**. A chemical substance that interacts with DNA and/or the cellular apparatus and thereby altering the integrity of the genome is classified as genotoxic. Non-genotoxic carcinogens do not interact directly with DNA, instead these enhance the tumor progression by affecting gene expression or cell proliferation. Weisburger in 1976 distinguished chemical carcinogens into three classes depending on their mechanism of action.

1. **Direct action or ultimate carcinogens:** Direct action or ultimate carcinogens are those whose structure confers them the capacity to induce cancer without a previous metabolic activation in the host organism. This category includes nitrosamines, epoxides, ethylene imines and  $\beta$ -propiolactone.
2. **Procarcinogens:** Procarcinogens includes the majority of chemical carcinogens which are initially non-carcinogenic but become active after metabolic processes i.e. become active only when it is metabolized in an organism. Some of the known procarcinogens are aminoazoic colorants, aromatic hydrocarbons, aflatoxins, aromatic amines and urethane.
3. **Co-carcinogens:** Co-carcinogens are chemical substances that have a helper role in carcinogenesis. They cannot induce cancer on their own, but can enhance the carcinogenic effect of other substances. In general, co-carcinogens act as promoters in tissues in which the initiation stage has appeared. Some of the co-carcinogens which help in promotion of cancer are coal tar, pesticides, hair dyes, tobacco, alcohol etc.

**Physical Carcinogens:** Physical carcinogens include radiation and non-radiation. Radiation includes both ultra violet (UV) light and ionizing radiation. Both the forms of radiation are implicated in causation of some forms of human cancers. In both the cases there is an appearance of mutation followed by a long period of latency after initial exposure which may be as long as 10 to 20 years or more. These radiations not only act as carcinogens (mutagens) but also act as co-carcinogens and may enhance the effect of carcinogens during the sequential stages of initiation, promotion and progression of the tumor.

UV radiation exerts its effect on cells by induction of mutation, inhibition of cell division, inactivation of enzymes, DNA damage and cell death. UV radiations of wavelength about 3000 Angstrom mainly cause skin cancers. As this type of radiation penetrate the skin up to few millimeters, so its effect is limited to epidermis. The efficiency of UV as a carcinogen depends upon the extent of light absorbing protective melanin pigment of the skin.

Ionizing radiations (X-rays, alpha, beta, and gamma rays, radioactive isotopes, protons and neutrons) have more penetrating power, therefore, may directly alter cellular DNA resulting in mutagenesis, cause chromosomal breakage, translocation or point mutations. It may also dislodge ions of water and other molecules of cell resulting into formation of reactive free radicals that may bring about molecular damage. These radiations can frequently cause leukemia and cancers of thyroid, skin, breast, ovary, uterus, lung, and salivary glands.

Non-radiation carcinogens are not in true sense some physical agent's rather certain mechanical injuries, for example injury from stones in gall bladder or urinary tract, healed scars following burns and tumors have been suggested as a cause of increased risk of carcinoma in the tissues. Other causes can be asbestosis and asbestos associated tumors of lung, implants of foreign inert materials like plastic, glass etc. in prosthesis. However, currently the evidences are not very convincing as far as implants are concerned.

**Biological Carcinogens:** These are biological agents like certain viruses, parasites, fungus or bacteria that can cause cancer. However, the role of viruses is more significant in causation of cancer. It has been estimated that around 20% of all the cancers worldwide are caused due to persistent virus infection.

Infection by a parasite *Schistosoma haematobium*, is associated carcinoma of urinary bladder, *Clonorchis sinensis*, a liver fluke cause's cholangiocarcinoma, the cancer of the bile duct. *Aspergillus flavus* and *Aspergillus parasiticus*, fungus best known for its colonization of cereal grains and legumes liberate significant quantities of toxic compounds generally termed as mycotoxins for example aflatoxin. Aflatoxins are poisonous and carcinogenic and their consumption is associated with development of hepatocellular carcinoma.

Many bacteria have also been reported as causal organism for cancer. *Helicobacter pylori* (*H pylori*) can cause ulcers and lead to stomach cancer.

*Salmonella typhi* is associated with gall bladder cancer, *Streptococcus bovis* with colorectal cancer, *Chlamydia pneumoniae* with lung cancer. Viruses as cancer causing agents have been divided into two groups: DNA oncogenic viruses and RNA oncogenic viruses. Both these viruses may induce mutation in the target host cell. RNA viruses (e.g. HIV, HCV) generally have very high mutation rate than DNA viruses. However, viral infection alone is not responsible for oncogenesis, yet it is one of the steps of a multi-step process of cancer development. Hepatitis viral infection has been associated with liver cancer and cervical cancer in women is caused by persistent infection with certain high-risk types of human papilloma virus (HPV).

These classifications are used by regulatory and scientific organizations to guide risk assessment, public health policy, and occupational safety.

International Agency for Research on Cancer (IARC) that is a part of World Health Organization (WHO) is involved in identification and classification of carcinogens. In the past 30 years, the IARC has evaluated the cancer-causing potential of more than 900 likely candidates, and has classified only a little over 100 chemicals as "carcinogenic to humans". They place the substances in one of the five groups (Table 13.2).

**Table 13.2: Classification of carcinogens as given by the International Agency for Research on Cancer (IARC) of WHO**

Group	Classification	Description
Group 1	Carcinogenic to humans	Sufficient evidence of carcinogenicity in humans
Group 2A	Probably carcinogenic to humans	Limited human evidence; sufficient animal evidence
Group 2B	Possibly carcinogenic to humans	Limited human evidence and less than sufficient animal evidence
Group 3	Not classifiable as to its carcinogenicity	Inadequate evidence in humans and animals
Group 4	Probably not carcinogenic to humans (rare)	Evidence suggests no carcinogenicity in humans or animals

## 13.5 DIAGNOSIS OF CANCER

Cancers are diagnosed in the biochemistry lab primarily by detecting specific biomarkers as discussed in the previous section, in bodily fluids like blood, urine, or biopsy tissue samples. As many carcinogens are also mutagens (cause mutations), Ames test can be used to screen for potential carcinogens. This test was developed in early 1970s by Bruce Ames and his group that is based on mutagenic activity of a substance. It is a rapid, cost-effective, and

widely used method and uses specific strains of *Salmonella typhimurium* that are unable to produce histidine due to mutations.

These bacteria are exposed to the chemical being tested, and if the chemical is mutagenic, it can cause a reverse mutation in the bacterial DNA, restoring the ability to produce histidine. This reversion allows the bacteria to grow on a medium lacking histidine, indicating a positive result for mutagenicity (Fig 13.4).

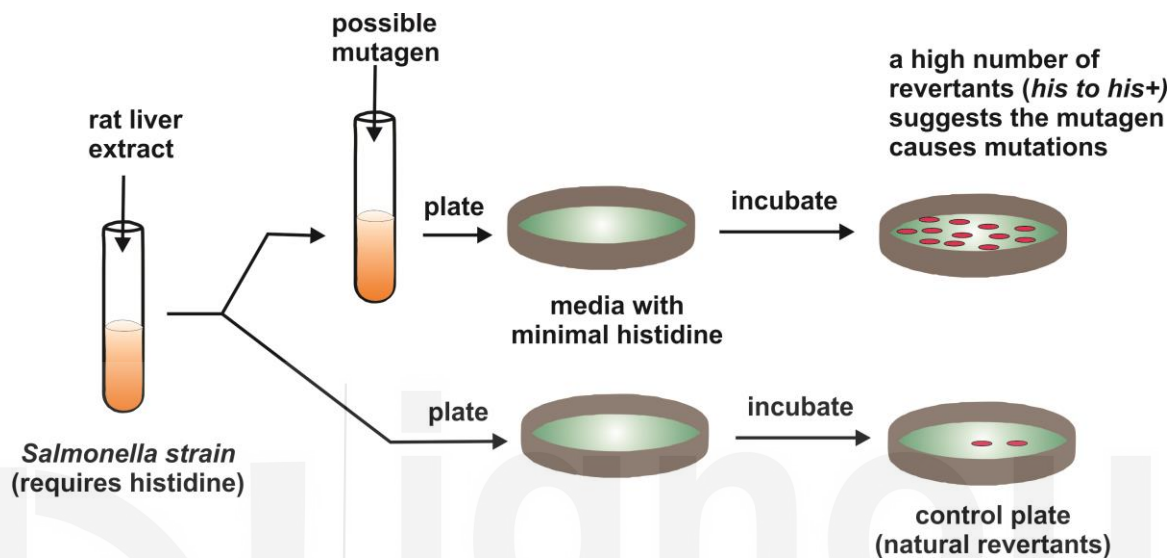


Fig 13.4: Ames test.

The Ames test is often used as one of the initial screens for potential drugs to weed out possible carcinogens, and it is one of the eight tests required under the Pesticide Act (USA) and one of the six tests required under the Toxic Substances Control Act (USA).

Biopsies involve taking a sample of tissue from a suspected tumor can be stained and examined under a microscope to look for cancer cells.

Many cancers are associated with abnormal activities of certain enzymes, which can be confirmed by biochemical testing, for example, elevated levels of alkaline phosphatase (ALP), particularly the placental isoenzyme, can be seen in some cancers, like liver and bone cancer. Similarly, changes in lactate dehydrogenase (LDH) isoenzyme patterns in cancer tissues can sometimes be detected in the blood.

Specific gene mutations or chromosomal abnormalities associated with cancer are confirmed with help of genetic testing that included techniques like PCR, FISH, and next-generation sequencing. These methods also detect the altered DNA methylation patterns and dysregulation of microRNAs (miRNAs) reported in cancers.

Although not under the preview of a biochemist, imaging techniques such as positron emission tomography (PET) scans, magnetic resonance imaging (MRI) and ultrasounds add valuable insights in the presence and progression of cancers. PET scans are used to detect areas of increased metabolic activity, which can be associated with cancer. Combining PET with CT scans provides anatomical and functional information. MRI can visualize soft tissues and is useful for detecting tumours in various organs. Ultrasound uses sound waves to create images of internal organs and can be used to detect tumours and assess their characteristics.

Advanced techniques involve use of various types of biosensors. Optical biosensors use light and electrochemical biosensors use electrical signals to detect changes in the concentration of biomarkers. Surface plasmon resonance (SPR) is a technique that measures changes in light reflection and can be used to detect biomolecular interactions.

Once cancer is diagnosed, lots of routine lab investigations are done to check the progression of cancer and effectiveness of its treatment.

Laboratory tests in patients with tumours include both routine tests as well as special examinations. Routine laboratory tests provide basic information about the patient's condition, nutrition, organ involvement due to the tumour growth or metastasizing of the tumour with consequent impairment of organ function, about any ongoing inflammatory reaction or change in condition following the use of effective therapy, action, tumour disease progression or the adverse effects of treatment.

Basic tests include blood count, basic urine tests and routine biochemical serum analysis. Cancer screening in patients over 50 includes blood in the faeces (faecal occult blood test) as part of the preventive medical check-up. Many alterations may already be seen in routine laboratory test results.

The blood count may exhibit signs of anaemia as a result of bleeding, chronic disease, malnutrition, iron or other factor deficiency, or bone marrow suppression after chemo and radiotherapy. Leukocytes may be increased not only in blood cell tumours (leukaemias) but also as a result of consequent infection or non-specifically as a reaction to the tumour, or, conversely, may be decreased if bone marrow is suppressed.

The basic biochemical serum analysis may also show various alterations:

Elevated inflammatory parameters due to infection or as a non-specific reaction to the cancer process

Signs of malnutrition – lowered albumin, prealbumin and cholinesterase

Elevated hepatic enzymes (ALT, AST, ALP, GGT) and bilirubin in liver injury, liver metastases and bile duct obstruction

Elevated urea, creatinine and potassium in kidney injury or as a result of urinary tract obstruction where the tract is compressed by the tumour

Elevated calcium in multiple myeloma or metastatic bone lesions

Elevated uric acid as a sign of tumour disintegration

Acid-base disorders in renal or pulmonary injury

Results of hormonal activity in endocrine-active tumours

The urine test may show haematuria that may accompany kidney and bladder cancer or glomerulopathies and urinary tract infections, or the presence of a protein as in myeloma (paraprotein). Non-typical tumour cells may be detected in the urine sediment

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## SAQ 2

Answer the following short answer questions:

- a) What is the difference between co-carcinogen and procarcinogen?
  - b) Write one example of each; physical carcinogen, chemical carcinogen and biological carcinogen.
  - c) Differentiate between genotoxic and non-genotoxic carcinogen.
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## 13.6 SUMMARY

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- Cancer is a multi-step process in which cells grow uncontrollably and invade the nearby tissues.
- Tumor is any abnormal growth of cells and is of two types: benign (non-cancerous) or malignant (cancerous). Tumors do not spread to other organs and are generally harmless.
- Depending on the type of tissue affected, cancers are broadly classified into four types: carcinoma, sarcoma, leukemia and lymphoma.
- Cancer is caused due to inherited genetic changes or epigenetic changes. Exposure to carcinogens like radiation, certain chemicals; unhealthy life style such as smoking or infections such as hepatitis B or C leads to liver cancer or certain infections may also lead to cancer. Human papilloma virus (HPV) causes cervical cancer.
- Cancer cells undergo morphological changes that include changes in nucleus, other cell organelle, cytoplasm, cell shape and surface. These changes in tissue biopsy of tissues with cancer when examined under microscope help in diagnosis of cancer.
- In addition to the morphological changes, cell undergo metabolic reprogramming to meet the demands of rapid cell division, resist cell death, and adapt to hypoxic conditions within the tumor microenvironment.
- Warburg effect is one of the well characterized metabolic alteration of cancer cells. The preference of cancer cells for glycolysis over oxidative phosphorylation, despite its lower efficiency in ATP production, is a hallmark of many types of cancer and is known as Warburg effect. Other metabolic changes involve increased glutaminolysis and *de novo* lipogenesis and changes in fatty acid oxidation.
- Tumor markers may be defined as quantifiable molecules, including DNA, RNA, proteins and metabolites, that are found in body fluids or tissues at an abnormal level that signal a pathologic condition, such as cancer. Some common examples are  $\alpha$ -fetoproteins and carcinoembryonic antigen.

- Carcinogens are substances that can induce or increase the risk of developing cancer. Inhalation, ingestion, application or injection of these carcinogens induce malignant tumours or increase their incidence or shorten the time of tumour occurrence. There are three broad categories of carcinogens; physical, chemical and biological.
- Cancer can be diagnosed by use of biochemical tests for detection of certain biomarkers, carcinogenic ability, imaging techniques and other advances biosensors.

## 13.7 TERMINAL QUESTIONS

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1. Discuss the methods used for cancer diagnosis.
2. State the role of biological agents in causing cancer with suitable examples.
3. Describe the metabolic changes in tumor cells and how does it help them grow? What is their clinical importance?

## 13.8 ANSWERS

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### Self-Assessment Questions

1.
  - a) AFP- Liver, ovarian and testicular cancer
  - b) CEA- Colon and rectum (colorectal or bowel cancer), Prostate, Ovary, Lung, Thyroid, Liver, Pancreas, Breast cancers
  - c) EGFR- Non-small cell lung cancer and colorectal cancer
  - d) BRAC gene mutations- Breast, ovarian, pancreatic, and prostate cancers
  - e)  $\beta$ -hCG- Choriocarcinoma and germ cell tumors
  - f) PSA- Prostate cancer
2.
  - a) Co-carcinogen: Co-carcinogens are chemical substances that have a helper role in carcinogenesis. They cannot induce cancer on their own, but can enhance the carcinogenic effect of other substances.  
  
 Procarcinogen- Procarcinogens includes the majority of chemical carcinogens which are initially non-carcinogenic but become active after metabolic processes i.e. become active only when it is metabolized in an organism.
  - b) Physical carcinogen- UV and ionizing radiation  
  
 Chemical carcinogen-epoxides and aromatic hydrocarbons  
  
 Biological carcinogen- HPV, Hepatitis B virus
  - c) A chemical substance that interacts with DNA and/or the cellular apparatus and thereby altering the integrity of the genome is classified as genotoxic. Non-genotoxic carcinogens do not interact directly with DNA, instead these enhance the tumor progression by affecting gene expression or cell proliferation.

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### **Terminal Questions**

1. Cancer is diagnosed with help of biochemical tests, molecular diagnostic methods like PCR and imaging techniques. Please refer to the section 13.5 for more details.
2. Biological agents that may lead to cancer are certain infectious viruses, parasites, fungus or bacteria, for example, *Helicobacter pylori* (*H pylori*) can cause ulcers and lead to stomach cancer. For more examples, please refer to the section 13.4.1.
3. Oncogenes and tumor suppressor genes rewire cellular metabolism to meet the demands of rapid cell division, resist cell death, and adapt to hypoxic conditions within the tumor cells. Please refer to the section 13.2.3 for details.

