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HUMAN CANCER GENETICS, GENOMICS & ITS PATHOGENESIS

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ABSTRACT

Cancer is characterized by uncontrolled cell growth and acquisition of metastatic properties. Tumors can be either benign (non cancerous) or malignant (cancerous). Four types of cancer involved like as Carcinoma, Sarcoma, Lymphoma, Leukemia and Myeloma. Acquired mutation and germline mutation is basic type of gene mutation. Many of the genes that involve into cancer development can be divided into several categories like tumor suppressor gene like p53 and BRCA1, oncogene like HER2 and RAS family gene. DNA repair genes mutation can be inherited or acquired. An example of the inherited form is Lynch syndrome. BRCA1, BRCA2 and p53 mutations and their associated syndromes are also inherited. Genomic information about cancer is leading to improve diagnoses and treatment plans that are tailored to patients' tumors, an approach called precision medicine. Two kinds of cancer variants are inherited variants and acquired variants. Transformation of normal cell into cancer cell in the multi-step process called as multi-step carcinogenesis. The phases of carcinogenesis included Initiation, Promotion, Progression, Metastasis. A cancer is linked to an increased risk of common mental disorders, which could have a negative impact on quality of life and survival.

1. INTRODUCTION

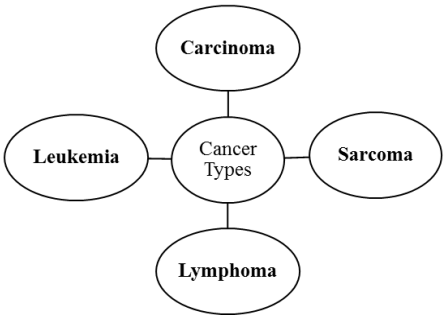
What is cancer?

Cancer is characterized by uncontrolled cell growth and acquisition of metastatic properties. In most cases, activation of oncogenes and/or deactivation of tumor suppressor genes lead to uncontrolled cell cycle progression and inactivation of apoptotic mechanisms.[1] The incidence of cancer and cancer types are influenced by many factors such as age, sex, race, local environmental factors, diet, and genetics.[12] People with cancer-prone inflammatory diseases, such as ulcerative colitis, haemochromatosis and viral hepatitis, have alterations in cancer-related genes and proteins, which are associated with free-radical stress.[2] As cancer cells divide and replicate itself, they often form a group of cancer cells called as a tumor.[13] Tumors can be either benign (non cancerous) or malignant (cancerous). Benign tumors can grow but do not spread or invade to surrounding tissues or other body parts. Malignant tumors can spread into, or invade to surrounding tissues.[14] Recent advances include the understanding that silencing is part of global epigenomic alterations in cancer, that pathways relevant to stem cell growth and differentiation become altered, and the approval of three drugs that target these defects in cancer patient.[3]

2. TYPES OF CANCER[4]

What Are the Different Types of Cancer?

Cancer is not just one disease but rather a group of diseases, all of which cause cells in the body to change and grow out of control. Cancers are classified either according to the kind of fluid or tissue from which they originate, or according to the location in the body where they first developed. In addition, some cancers are of mixed types.



The following five broad categories indicate the tissue and blood classifications of cancer:

1. Carcinoma[4]

A carcinoma is a cancer found in body tissue known as epithelial tissue that covers or lines surfaces of organs, glands, or body structures. For example, a cancer of the lining of the stomach is called a carcinoma. Many

carcinomas affect organs or glands that are involved with secretion, such as breasts that produce milk. Carcinomas account for 80-90% of all cancer cases.

Types of carcinoma include

A. Melanoma
B. Basal cell carcinoma
C. Squamous cell skin cancer
D. Merkel cell carcinoma

A. Melanoma

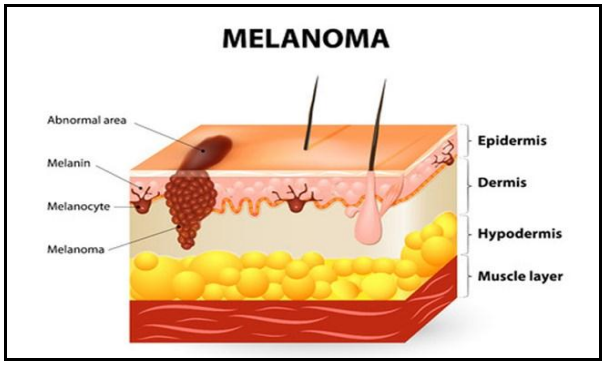


Figure no 1: Melanoma.

Melanoma is a melanocytic skin cancer that occurs after mutation of DNA, most often secondary to excess sun exposure. People with Fair-skinned and light-haired living in high sun-exposure environments are at highest risk. Clinically, melanoma exhibits irregular shape, irregular color, and asymmetry. Sometimes, melanoma exhibits ulceration and bleeding, which are associated with a poorer prognosis. A punch biopsy often reveals atypical nests of melanocytes that accumulate and coalesce at the dermo-epidermal junction. The depth of melanoma is the most important prognostic factor. Two staging systems are available to assess depth: Breslow and Clark levels. In the past, physicians used the Clark level. However, Breslow level is now the standard of care because it is more specific.[5]

B. Basal cell carcinoma[4]

Basal cell carcinoma (BCC), previously known as basal cell epithelioma, is the most common cancer in Humans. BCC mostly arises on sun-damaged skin and rarely develops on the mucous membranes or palms and soles. Basal cell carcinoma is usually a slow-growing tumor for which metastases are rare. Although rarely fatal, BCC can be highly destructive and disfigure local tissues when treatment is inadequate or delayed. On clinical examination, BCC usually appears as flesh- or pink-colored, pearly papules with overlying ulceration or telangiectatic vessels. BCC occurs on the head or neck in the majority of cases, but can involve the trunk and extremities.[6]

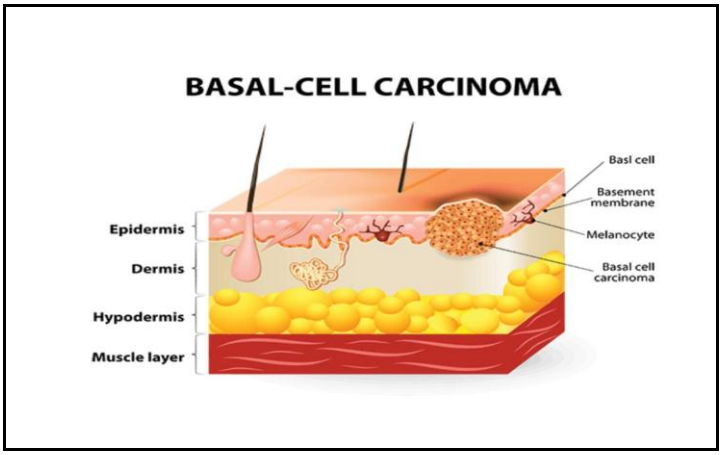


Figure no 2: Basal cell carcinoma.

C. Squamous cell skin cancer [4]

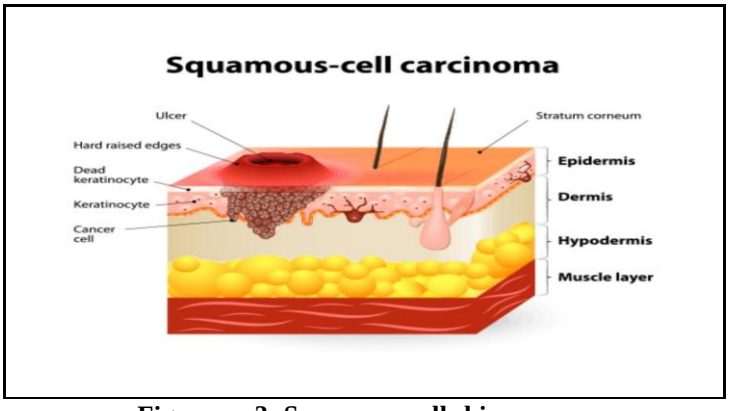


Figure no 3: Squamous cell skin cancer.

Cancer that begins in squamous cells. Squamous cells are thin, flat cells that look like fish scales, and are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the lining of the respiratory and digestive tracts. Most cancers of the anus, cervix, head and neck, and vagina are squamous cell carcinomas. Also called epidermoid carcinoma.[7]

D. Merkel cell carcinoma[4]

Merkel cells are found in the top layer of the skin. These cells are very close to the nerve endings that receive the sensation of touch. Merkel cell carcinoma, also called neuroendocrine carcinoma of the skin or trabecular cancer, is a very rare type of skin cancer that forms when Merkel cells grow out of control. Merkel cell carcinoma starts most often in areas of skin exposed to the sun, especially the head and neck, as well as the arms, legs, and trunk.[8]

2. Sarcoma

Sarcoma is a malignant tumor growing from connective tissues, such as cartilage, fat, muscle, tendons, and bones. The most common sarcoma, a tumor on the bone, usually occurs in young adults. Examples of sarcoma include osteosarcoma (bone) and chondrosarcoma (cartilage).

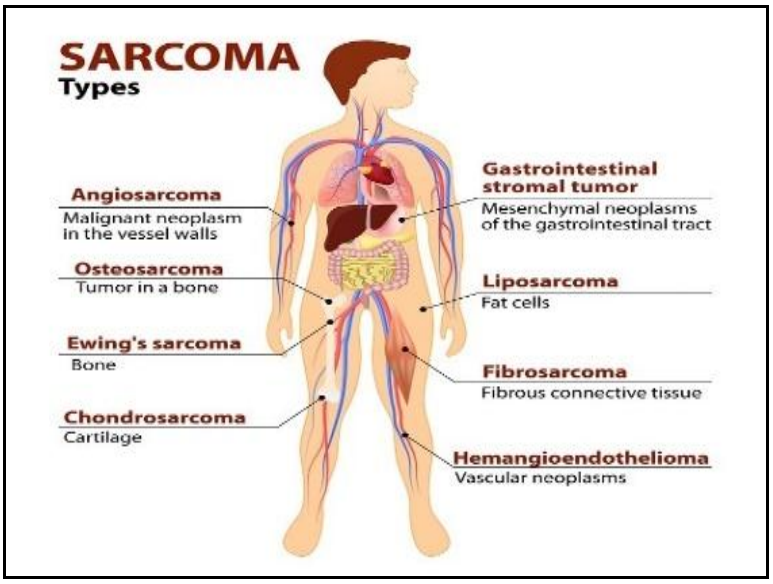


Figure no 4: Sarcoma.

Types of sarcoma include

A. Soft tissue sarcoma
B. Osteosarcoma
C. Ewing's sarcoma
D. Chondrosarcoma

A. Soft tissue sarcoma

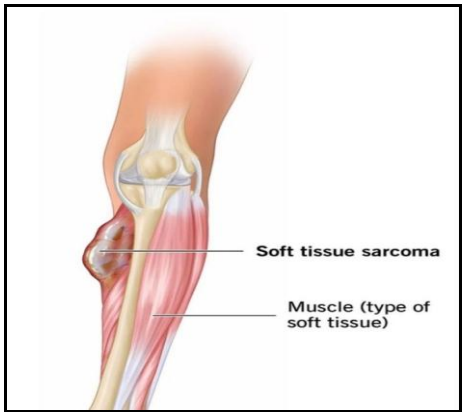


Figure no 5: Soft tissue sarcoma.

Soft-tissue sarcoma (STS) is a diverse group of rare cancers that are caused by pathological transformations within the mesenchyma, which is the mesodermal part of the embryo that develops into connective and skeletal tissues [15]. Soft tissue sarcoma commonly forms in the body's muscles, joints, fat, nerves, deep skin tissues, and blood vessels.[16] Soft tissue sarcomas can occur in any part of body, but most occur at the extremity (59%), the trunk (19%), the retroperitoneum (15%), or the head and neck (9%).[17]

B. Osteosarcoma

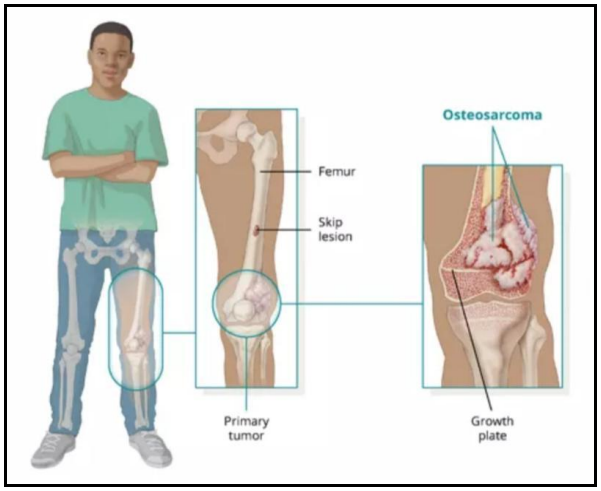


Figure no 6: Osteosarcoma.

Osteosarcoma (also called osteogenic sarcoma) is a type of bone cancer that develops in the osteoblastic cells that form the outer cover of the bone. It occurs most commonly in children, adolescents, and young adults.[18] The incidence of OS is commonly found in the metaphysis of long tubular bones (such as the proximal humerus, the distal femur, and the proximal tibia), but rare in the spine, pelvis, and sacrum areas.[19] Prognostic factors for osteosarcoma such as tumor site, tumor size, respectability of tumor, histological response to chemotherapy, and presence of metastases, with unilateral lung metastases having better prognosis.[20]

C. Ewing's sarcoma

Ewing sarcoma is the second most common bone tumor in children and adolescents. Ewing sarcoma can develop in both bone and soft tissue, with the lower extremity and pelvis being the most common osseous sites and trunk and extremity the most common extra osseous sites. Ewing sarcoma most commonly occurs in white adolescents, with a median age of 15 years.[21] Ewing's sarcoma has mostly non-specific clinical characteristics. Patients may Report localized pain, which may be accompanied by swelling that can be mistaken for a minor injury. The pain is frequently modest and occasionally get worse at night or after exercise, although some patients do not have pain at all.[22]

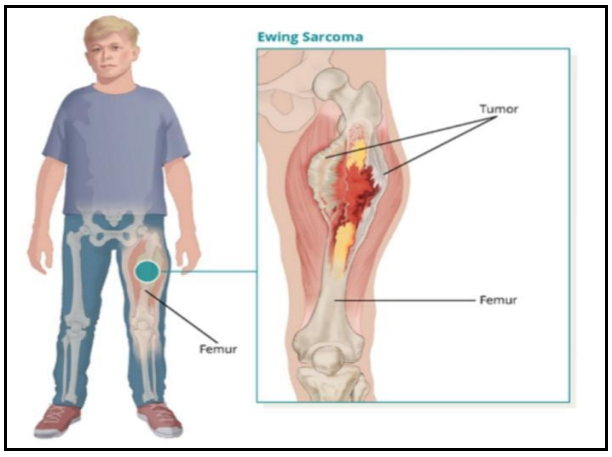


Figure no 7: Ewing's sarcoma.

D. Chondrosarcoma

Chondrosarcomas are malignant cartilaginous neoplasms with wide range of morphological features and clinical behaviour. They frequently start in the pelvis or long bones.[23] The most common treatment is surgery to remove malignant tissue and bone. After five years' diagnosis, approximately 60% to 70 % of people who have the most common form of chondrosarcoma are alive.[24]

3. Lymphoma

Lymphoma refers to a cancer that originates in the nodes or glands of the lymphatic system, whose job it is to produce white blood cells and clean body fluids, or in organs such as the brain and breast. Lymphomas are classified into two categories: Hodgkin's lymphoma and non-Hodgkin's lymphoma.

Types of lymphoma include

A. Hodgkin's lymphoma
B. Non-Hodgkin's lymphoma
C. Cutaneous lymphoma

A. Hodgkin's lymphoma

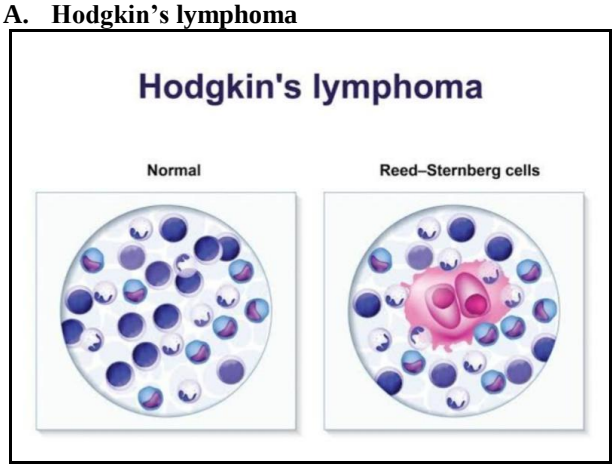


Figure no 8: Hodgkin's lymphoma.

Hodgkin lymphoma (HL) is a rare lymphatic tumour is one of the most common cancers in young adults. The disease is characterized by low number of B-lymphocytes derived malignant cells and an extensively inflammatory Microenvironment. Histopathologically, 95% of HL cases are classified as cHL including the sub types of Nodular sclerosis, mixed cellularity, rich lymphocyte and lymphocyte-depletion HL. In 5% of cases, NLPHL is diagnosed.[25]

B. Non-Hodgkin's lymphoma

Non-Hodgkin lymphomas are a type of cancers that arises from abnormal lymphoid tissue proliferation. The neoplastic cells are thought to have originate from a single clone of lymphocytes, similar to Chronic Lymphocytic Leukaemia; however, in NHL, the morphology of cells may vary. Malignant B lymphocytes are cause of Non-Lymphoma Hodgkin's in 85% of cases, while T lymphocytes are responsible for the remaining 15%.[26]

C. Cutaneous lymphoma

Cutaneous lymphomas (CLs) are an uncommon and diverse group of lymphoma that present in the skin without extracutaneous manifestations at the time of diagnosis.[27] Primary cutaneous lymphomas, a type of non-Hodgkin lymphomas, are the most common type of extra nodal lymphomas except for those that occur in the gastrointestinal tract. In addition, current and future molecular targets for cutaneous lymphomas are discussed, with a special emphasis on mycosis funogides (MF) and Sézary syndrome (SS). In the most recent classification, two types of cutaneous lymphomas were added as provisional entities: (1) chronic EBV-positive

mucocutaneous ulcer and (2) primary cutaneous acral CD8+ T cell lymphoma.[28]

4. Leukaemia

Leukaemia, also known as blood cancer, is a cancer of the bone marrow that keeps the marrow from producing normal red and white blood cells and platelets. White blood cells are needed to resist infection. Red blood cells are needed to prevent anemia. Platelets keep the body from easily bruising and bleeding. Examples of leukaemia include acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, and chronic lymphocytic leukemia. The terms myelogenous and lymphocytic indicate the type of cells that are involved.

Types of leukemia included

A. Acute lymphocytic leukemia
B. Acute myeloid leukemia
C. Agnogenic myeloid leukemia
D. Chronic lymphocytic leukemia
E. Chronic myeloid leukemia
F. Essential thrombocythemia (ET)
G. Hairy cell leukemia
H. Myelodysplastic syndromes (MDS)

A. Acute lymphocytic leukemia

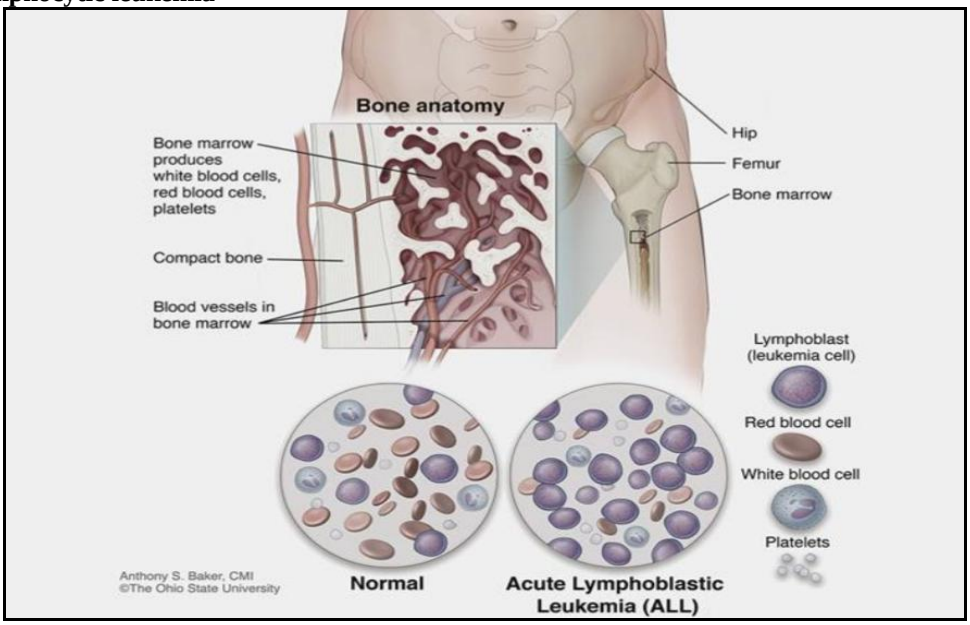


Figure no 9: Acute lymphocytic leukemia.

Acute Lymphocytic Leukemia also known as Acute Lymphoblastic Leukemia. Acute Lymphocytic Leukemia (ALL) is a malignancy of B or T lymphoblast. The disease pattern associated with acute lymphocytic leukemia is characterized by uncontrolled proliferation of abnormal, immature lymphocytes and their progenitors which ultimately result in the replacement of bone marrow components and other lymphoid organs. Acute Lymphocytic Leukemia affect males slightly more than females, and three times as frequently in Whites as in Blacks. Symptoms such as fatigue, easy or spontaneous bruising/bleeding, and infections. B-symptoms, like as fever, night sweats, and unintentional weight loss are common but may be mild.[29]

B. Acute myeloid leukemia

Acute myeloid leukemia (AML) is a malignant neoplasm characterized by immature, Bone marrow (BM)-derived myeloid cells with variable differentiation. AML is a biologically heterogeneous disease group that most commonly affect the BM and peripheral blood (PB) but it can also affect extramedullary tissue[30].The risk factors of AML such as male gender, older age, smoking, exposure to chemicals (benzene, Formaldehyde), chronic myeloproliferative neoplasms (polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis), myelodysplastic syndrome (MDS), high-dose radiation exposure, chemotherapeutic drugs (alkylating agents, topoisomerase II inhibitors), genetic syndromes (eg, Fanconi anemia, Bloom syndrome), and family history of AML.[30]

C. Agnogenic myeloid leukemia

Agnogenic myeloid leukemia is also known as primary myelofibrosis, chronic idiopathic myelofibrosis(CIMF), idiopathic myelofibrosis, myelofibrosis with myeloid metaplasia. Agnogenic myeloid leukemia is a rare bone marrow disorder that is characterised by irregularities in the synthesis of blood cells (haematopoiesis) and scarring (formation of fibrous tissue) within the bone marrow. In primary myelofibrosis, a single hematopoietic stem cells altered the DNA leads the abnormal cell to continually self replicate. Eventually, these abnormal cells crowd out normal, healthy cells in the marrow and interfere with the production of RBCs, WBCs and platelets.[31]

D. Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a lymphoid malignancy characterised by the proliferation and accumulation of mature CD5+ B cells in the blood, bone marrow and lymph nodes.[32] In CLL, excessive number of blood stem cells become abnormal lymphocytes. The abnormal lymphocytes may also have known as leukemia cells. Infection resistance is very weak in these leukemia cells. CLL is one of the most typical form of leukemia in adults. It frequently occurs during or after middle age; children are rarely affected by it.[33]

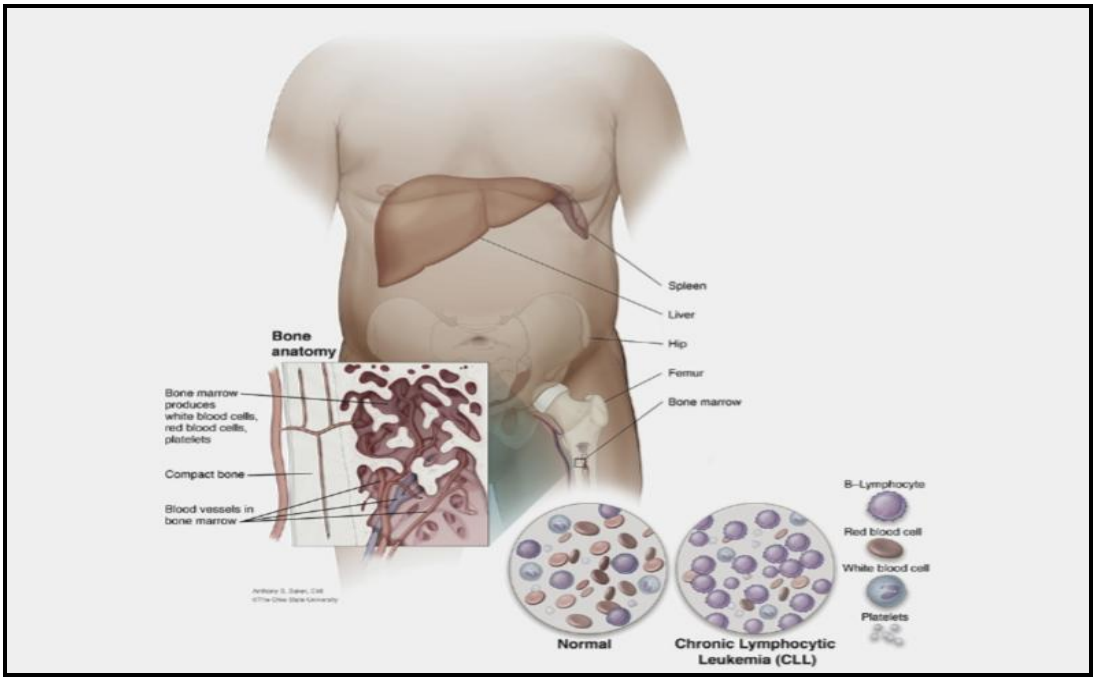


Figure no 10: Chronic lymphocytic leukemia.

E. Chronic myeloid leukemia

White blood cell cancer known as Chronic myelogenous leukemia (CML), it is also called as chronic myeloid leukemia. It is a specific type of leukemia characterised by the overproduction and uncontrolled growth of myeloid cells in the bone marrow and the proliferation of myeloid cells in the blood. CML is a clonal bone marrow stem cell condition in which a proliferation of mature granulocytes (neutrophils, eosinophils and basophils) and their progenitor is found. It is a particular variety of myeloproliferative neoplasm link with a distinctive chromosomal translocation known as Philadelphia chromosome.[34]

F. Essential thrombocythemia

Essential thrombocythemia (ET) is also called as chronic myeloproliferative neoplasm (MPN) characterised by an increased platelet count. Thrombosis and bleeding both are the clinical effect of uncontrolled thrombocytosis. ET has the best prognosis of these conditions but it is characterised by significant clinical heterogeneity, and the minority of individual who acquired progressive myelofibrosis or acute myeloid leukemia have a much poorer outlook. Proliferative alteration in the bone marrow and demonstration of clonality are used to diagnose the ET.[35]

G. Hairy cell leukemia

Hairy cell leukemia (HCL) is a relatively uncommon chronic B-cell cancer that affect the bone marrow, spleen, and peripheral blood. Pancytopenia which includes monocytopenia, may be found during complete blood count. Hairy cell leukemia is an uncommon neoplasm representing 2% of lymphoid leukaemia's. Average age of patient is 55 old at diagnosis. Although it may affect the younger people, it is rarely occurring in children.[36]

H. Myelodysplastic syndromes (MDS)

MDS is also known as myelodysplasia. The term "Myelodysplastic syndrome (MDS) is refers to a diverse group of hematologic neoplasm that is typically cause a dysplasia and ineffective haematopoiesis in the bone marrow due to clonal disorder of hematopoietic stem cells. Acute myeloid leukemia (AML) may develop in Some MDS patients. Patients over 65 years old are typically diagnosed with MDS.[37]

Myeloma

Myeloma develop in the plasma cells of bone marrow. Sometimes, the myeloma cells gather in one bone and produce a single tumor, known as plasmacytoma. However, in some cases, the myeloma cells gather in many bones, resulting in many bone tumors. This disease known as multiple myeloma.

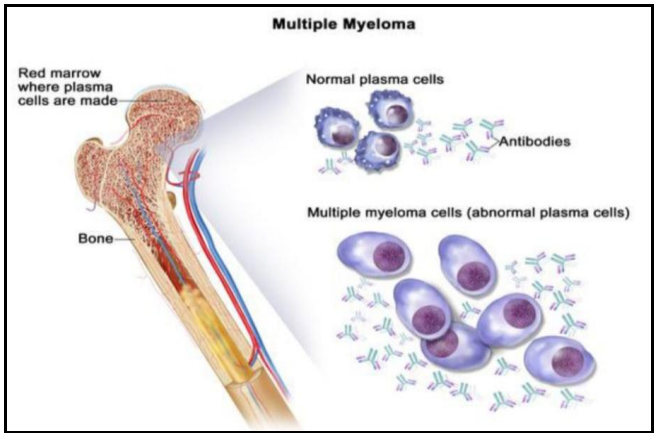


Figure no 11: Myeloma.

3. GENES INVOLVED IN CANCER[9]

There are 2 basic types of genetic mutations

A. Acquired mutations

These are the most typical cancer causing factor. They develop from damage to genes in a specific cell during a person's life. For example, this could be a breast cell or a colon cell, which subsequently divide many times and develop a tumor. An unusual lump is tumor. Cancer that develop from acquired mutations is called sporadic cancer. Every cell in the body are not have acquired mutations and they are not passed from parent to child.

The following factors can result in these mutations

- Tobacco
- Ultraviolet (UV) radiation
- Viruses
- Age

B. Germline mutations

These are less common. Sperm cell or egg cell can produce a germline mutation. During conception, it is directly from a parent to a child. As the embryo develop into a baby, the mutation from the initial sperm or egg cell is replicate into all cell of the body. Because the mutation affects reproductive cells, it can spread from generation to generation. Cancer caused by germline mutations also known as inherited cancer. It accounts between 5% to 20% of all malignancies.

Types of genes linked to cancer

Many of the genes that involve into cancer development can be divided into several categories

Tumor suppressor genes.

These are protective genes. Normally, they prevent cell growth by

- Monitoring how quickly cells divide into new cells
- Repairing mismatched DNA
- Controlling when a cell dies

A tumor suppressor gene mutation causes uncontrollable cell growth. And additionally they may develop into a tumor. Examples of tumor suppressor genes include *BRCA1*, *BRCA2,* and *p53* or *TP53*.Germline mutations in *BRCA1* or *BRCA2* genes the hereditary breast or ovarian cancers occur in woman's and hereditary prostate or breast cancers occur in man. In both women and men raise the risk of pancreatic cancer and melanoma. p53 or TP53 is the gene that is most frequently mutated gene in Cancer patients. A damaged or missing *p53* gene is present in over a 50% of malignancies. Mutation of *p53* gene are acquired. Germline *p53* mutations are uncommon, but patients who have them increased a chance of developing wide range of cancer.

Oncogenes.

A healthy cell becomes a cancerous cell as a result of them. Inheritance of these gene mutations is unknown.

Two common oncogenes are

i. HER2, a specialized protein that regulate development and dissemination of cancer. It is present in some cancer cells. For example, breast and ovarian cancer cells.

HER2 in Breast Cancer

Human epidermal growth factor receptor 2 (HER2) is a proto-oncogene which is situated on chromosome 17 at q21 and the epidermal growth factor receptor with Tyrosine kinase activity. In Breast cancers, HER2 gene amplification is 15%–20% of invasive breast cancers and this amplification is closely related to HER2 protein overexpression. Patients with breast cancer, HER2 amplification is a poor prognostic factor that is linked to high risk of recurrence and mortality, and is a predictor of responsiveness to anthracyclinebased chemotherapies.[38]

The **RAS** family of genes, produce proteins that are involved in cell growth, and cell death cell communication pathways. The RAS superfamily of small GTPases are guanine nucleotide dependent molecular switches to control a several cellular activities. With more than 15 family members, the superfamily can be divided into five smaller subfamilies—Ras, Rho, Ran, Rab, and Arf-depend on their sequence, structural similarity, and functions in the cell. Ras proteins cycle within the cell between an inactive GDPbound form and

an active GTP-bound state, whereupon the GTPases can attached to effectors and control cellular functions.[39]

ii. DNA repair genes

These correct errors that occur when DNA is copied. They all serve as tumor suppressor genes in various ways. DNA repair genes included *BRCA1*, *BRCA2*, and *p53*.If a person has a defect in a DNA repair gene, mistakes are not corrected. Then, the error turns into mutations. Particularly mutations in tumour suppressor genes or oncogenes may eventually result in cancer.DNA repair genes mutation can be inherited or acquired. An example of the inherited form is Lynch syndrome. *BRCA1*, *BRCA2* and *p53* mutations and their associated syndromes are also inherited.

BRCA1

Linkage analysis was used to identify BRCA1 as gene associated with an early-onset breast cancer in affected families. A large protein of 1,863 amino acids41 and several functional domains is encoded by the BRCA1 gene.[40] Missense mutations in breast cancer susceptibility protein 1 (BRCA1) and its obligate binding partner BRCA1-associated RING domain protein (BARD1) have been related to familial breast and ovarian cancers as well as sporadic cancers of various origins. The N-terminal RING domains of BRCA1 and BARD1 enable heterodimerization.[41] BRCA1 and BARD1 together function in DNA repair, replication fork protection, transcription and tumour suppression.[40]

BRCA2

The BRCA2 gene was firstly discovered as a breast cancer susceptibility located on chromosome 13. In fact, further studies have indicated that heterozygous germline mutations in BRCA2 are associated with an increased lifetime risk of cancers in organs of epithelial origin, such as the breast, ovaries, pancreas and prostate. The main mediator protein in human cell is BRCA2, is essential for DNA repair. Human BRCA2 is required for the maintenance of chromosome integrity, by functioning in stabilizing stalled DNA replication forks, or in mitotic cell division. Inheritance of two hypomorphic BRCA2 alleles can occur in a rare syndrome is called as Fanconi anaemia (FA). This syndrome is described by congenital defects, progressive bone marrow failure, hypersensitivity to DNA mutagens and susceptibility to cancer.[42]

p53

The TP53 protein which encoded by the p53 gene, functions to inhibit the growth of cancer. The TP53 gene, which produces the p53 protein, is located on chromosome 17p13.1.[43] This transcription factor control key gene that are included in cell function and carcinogenesis, such as apoptosis, senescence, and DNA repair.[44] An oligomerization domain, a transactivation and proline rich domain, a central DNA-binding domain (DBD) is a three functional domains of the p53 protein.[45]

4. CANCER GENOMICS[10]

Genomic information about cancer is leading to improve diagnoses and treatment plans that are tailored to patients' tumors, an approach called precision medicine. As a result of research into the genomic changes connected with cancer, drugs have been developed to fight the disease in several ways:

- Inhibiting enzymes that causes the abnormal growth and survival of cancer cells
- Preventing aberrant gene expression characteristic of cancer cells
- Reducing molecular signaling pathways that are in hyperactive in cancer cells

Two kinds of cancer variants[11]

Simply put, cancer is a genomic disease. It occurs when modification in a person's genome - their DNA - cause uncontrollable cells growth and division. These genomic modifications or variations may be inherited from a parent or acquired at some point during a person's lifetime. Acquired genomic variants are main cause of cancer. In about 5% of cases, however, the person has inherited a variant that greatly raise their chances of developing cancer.

Inherited (germline) genomics variants vs acquired (somatic) variants

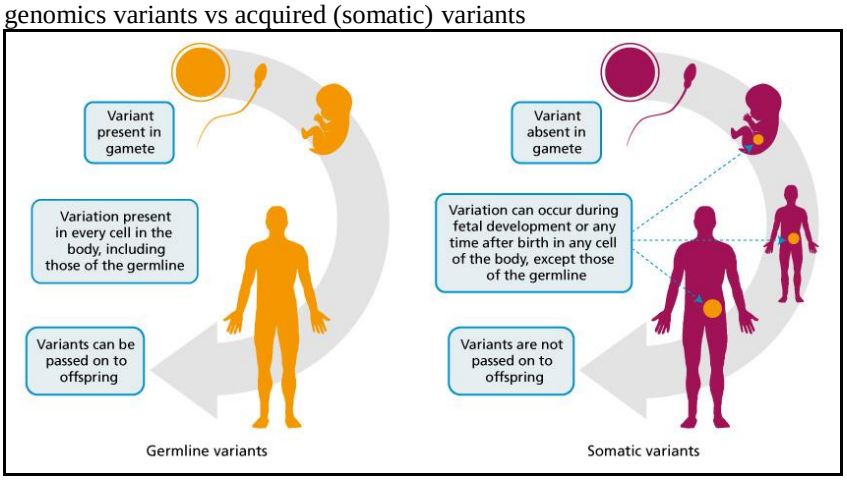


Figure no 12: Germline and Somatic cancer variants.

Two kinds of cancer variants

A. Inherited variants

Inherited genomic variants are also known as germline variants. These variants are found in almost all of a person's cells, and some uncommon variations raise the chances of cancer in an individual. It is important to recognise when a patient has this type of germline variant, as it can impact for their clinical care. A patient with this kind of variant may be given to the option of additional screening or prophylactic surgery. For example, patients with specific *BRCA1* and *BRCA2* gene variation may choose to undergo a preventative mastectomy or oophorectomy. It is also important to consider the effect on the patient's family; as appropriate testing can identify other at-risk relatives who may be able to take precautions of developing cancer.

B. Acquired variants

Acquired genomic variants also known as somatic variants, and these variants are found only in cancer cells. These variants cannot be passed on to any offspring because they are not inherited. Somatic variants can be developing from the exposure to environmental factors, like as smoking, radiation, alcohol and UV light or they can be developing random. At a time of cell divides, errors can be occurring. While there is numerous process in the cell to repair these errors, sometimes they are missed.

5. PATHOGENESIS OF CANCER[46]

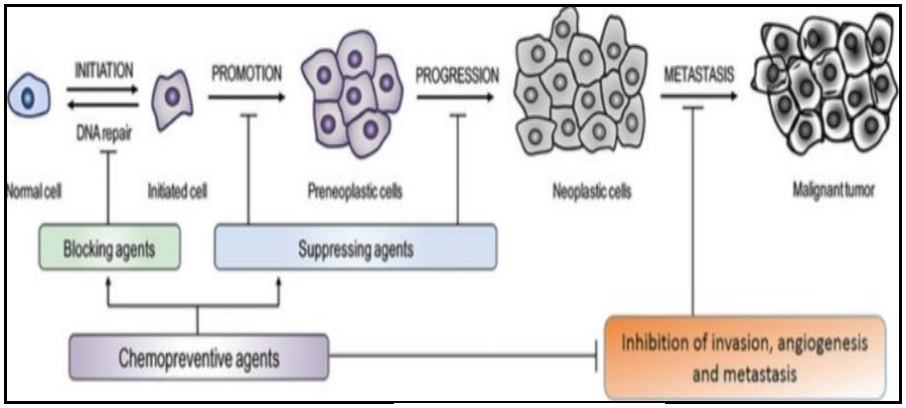


Figure no 13: Pathogenesis of cancer.

Transformation of normal cell into cancer cell in the multi-step process called as multi-step carcinogenesis. The phases of carcinogenesis included:

- Initiation
- Promotion
- Progression
- Metastasis

- **Initiation**

Initiation included the alteration, modification or mutation of genes that develop spontaneously or induced by exposure to a carcinogenic substance. Genetic changes can leads to dysregulation of biochemical signaling pathways involved in cellular proliferation, survival, and differentiation. This pathway are influenced by a number of factors, such as the rate and type of metabolism of carcinogen and the response of the DNA repair function.

- **Promotion**

The promotion phase is considered to be a relatively long and reversible process in which actively proliferate accumulation of paraneoplastic cells. Within this period, the process may be altered and growth rate affected by chemo preventive agents. Progression is the stage between a premalignant lesion and invasive cancer development.

- **Progression**

Progression is the final phase of neoplastic transformation, during which genetic and phenotypic changes as well as cell proliferation takes place. This included a rapid growth in the tumor size, where the cells may be resulting mutations with invasive and metastatic potential. Chemopreventive agents should be able to preferentially act between the beginning and progression of carcinogenesis.

- **Metastasis**

Metastasis is the process in which cancer cells from the initial site to other regions of the body via the bloodstream or the lymphatic system. Chemopreventive agents are known to prevent angiogenesis and invasion of primary tumors, and they could be used to prevent the metastasis of cancer.

6. CANCER CURRENT IMPACT ON HUMAN BEING

Patients suffering from cancer with greater risk of mortality. It has significant effects on mental health, and depression and anxiety. A cancer is linked to an increased risk of common mental disorders, which could have a negative impact on quality of life and survival.[47] It can impair daily function and lead to negative impacts on quality life, self-care abilities of patients.[48]

CONCLUSION

This review article is composed of series events to be occur inside every suffering human being. As Cancer is uncontrolled irregular growth of cancer cells the major pathogenesis, causative factor is cover under this review. Again tumor suppressor genes include BRCA1, BRCA2, and p53 or TP53.Germline mutations in BRCA1 or BRCA2 genes the hereditary breast or ovarian cancers occur in woman's cover under this heading. Transformation of normal cell into cancer cell in the multi-step process called as multi-step carcinogenesis this steps involved Initiation, Promotion, Progression, Metastasis.

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