Epidemiology of cancer

Incidence of cancer is depended on several factors:-

1- Environmental factors :- Environmental exposures are the dominant risk factors for many common cancers, this suggesting that a high fraction of cancers are potentially preventable.
For instance,
Death rates from breast cancer are 4 - 5 times higher in the United States than in Japan. Death rates from colonic cancer are higher in the United States than in Japan. Conversely, the death rate for gastric cancer is 7 times higher in Japan than in the United States. Japanese living in the United States incidence of both cancers is intermediate between Japanese and USA natives .
Liver cell carcinoma is relatively infrequent in the United States but is the most lethal cancer in African .

The most important environmental predisposing factors to cancer
1- ***Diet* :-** obesity, increased risk for developing many different cancers .
2- ***Smoking.*** Smoking of cigarettes, lead to cancer of the mouth, pharynx, larynx ,esophagus, pancreas, bladder, and the lung .
3- ***Alcohol consumption.*** Alcohol abuse is a risk factor for cancers of the pharynx, larynx, esophagus, and liver.
4- ***Reproductive history.*** accumulative exposure to estrogen stimulation, increases the risk for developing cancers of the endometrium and breast .
5- ***Infectious agents.*** infectious agents cause approximately 15% of cancers in the world .

2-Age:- The frequency of cancer increases with age (55-75 years). The rising incidence with age may be explained by **the accumulation of somatic mutations that drive the emergence of malignant neoplasms** and **The decline in immune activity that accompanies aging .**

The major lethal cancers in children are leukemias , tumors of the central nervous system, lymphomas.

3- Acquired Predisposing Conditions :- Acquired conditions that predispose to cancer include disorders associated with :-

- Chronic inflammation:- Many chronic inflammatory conditions create a fertile “soil” for the development of malignant tumors are mostly carcinomas , mesothelioma and lymphoma .

- Immunodeficiency states:- immunodeficiency states mainly predispose to virus-induced cancers .

- precursor lesions :- are localized disturbances of epithelial differentiation that are an elevated risk for developing carcinoma . They may arise secondary to chronic inflammation or hormonal disturbances , or may occur spontaneously .

The precursor lesions include :

1- Squamous metaplasia and dysplasia of bronchial mucosa, seen in smokers—a risk factor for lung carcinoma .

2- Endometrial hyperplasia and dysplasia, seen in women with estrogenic stimulation—a risk factor for endometrial carcinoma.

3- Leukoplakia of the oral cavity which may progress to squamous cell carcinoma .

4- Villous adenoma of the colon ,is a high risk for progression to colorectal carcinoma .

The subsequent development of malignancy from benign tumor is uncommon there are few exceptions, e.g., villous adenoma of the colon often develops into carcinoma.

PREINVASIVE MALIGNANCY (Dysplasia) :

Dysplasia is disorganization of tissue structure . Dysplastic tissue share some cytological features of infiltrative (malignant) tumors , but have not yet become infiltrative . become infiltrative if left long enough .

Dysplasia have been described in the epithelia of the
-cervix
-vulva
-urinary bladder
-bronchial mucosa
-larynx
-oral cavity
-skin
-prostate etc .
In the cervix, vulva and the prostate they are called "intraepithelial neoplasia".

The dysplastic cells show many of the cytological changes of malignant tumors , like (cellular overcrowding , pleomorphism , hyperchromatic nuclei , loss of normal orientation (loss of polarity) and , mitotic activity) above the basal layers .
Despite these manifestations of abnormal cell behavior, the all changes are confines within the normal epithelium; the basement membrane is not breached .
When the entire thickness of the epithelium is involved by these cellular changes , this has been referred to as **"carcinoma in situ"** grade 3 .
Carcinoma in situ is the forerunner of invasive malignancy , However mild degrees of dysplasia (grade 1 or low-grade intraepithelial neoplasia) , common in the uterine cervix, don't always lead to cancer and are often reversible .

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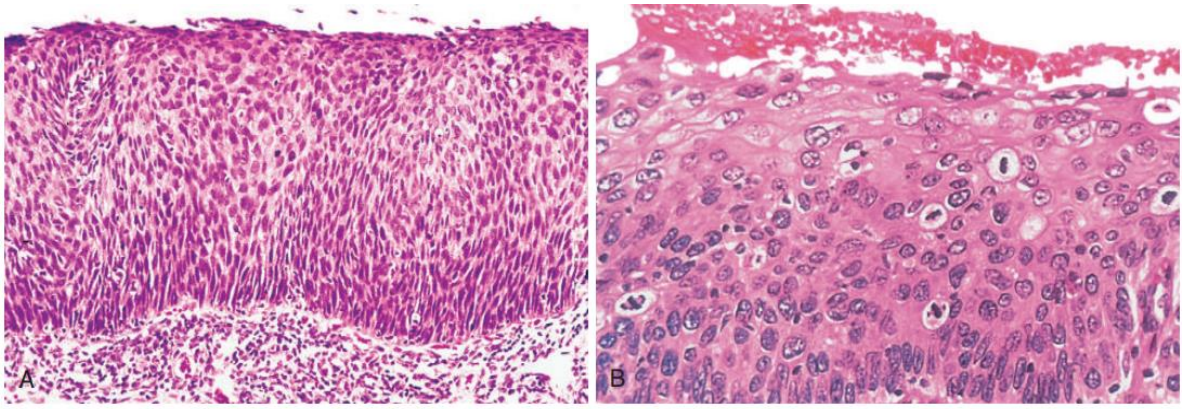


Carcinoma in situ. (A) Low-power view shows that the entire thickness of the epithelium is replaced by atypical dysplastic cells. There is no orderly differentiation of squamous cells .The basement membrane is intact, and there is no tumor in the subepithelial stroma. (B) High-power view of another region shows failure of normal differentiation, marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface. The intact basement membrane (below) is not seen in this section.

Etiology of cancer: carcinogenic agents

1- Chemicals. that directly damage DNA, leading to mutations and eventually cancer .
Direct-acting agents do not require metabolic conversion to become carcinogenic, while **indirect-acting agents** are not active until converted to carcinogenic by endogenous metabolic pathways .

2- Radiant energy. As UV rays leading to mutations. Therefore UV rays can give rise to squamous cell carcinomas and melanomas of the skin .

3- Microbial agents

A-Oncogenic RNA Viruses as human T-cell leukemia virus-1 (HTLV-1) which cause T-cell leukemia /lymphoma .

B-Oncogenic DNA Viruses as Human Papillomavirus and Hepatitis B and Hepatitis C Viruses .

C-Helicobacter pylori which cause of peptic ulcers , gastric adenocarcinomas .

The Molecular Basis of Cancer (Carcinogenesis)

Fundamental principles

There is some fundamental principles before delving into the details of the genetic basis of cancer .

1-Nonlethal genetic damage

Nonlethal genetic damage (or mutation) lies at the heart of carcinogenesis . Such genetic damage may be :-

A- acquired by the action of environmental agents, such as chemicals, radiation, or viruses.

B- inherited in the germ line .

The genetic hypothesis of cancer implies that a tumor mass results from the clonal expansion of a single progenitor cell that has incurred genetic damage (i.e., tumors are monoclonal).

progenitor cell is that cell from which another cell or a family of cells (clone) is descended .

2- Target genetic damage

Four classes of **normal regulatory genes** are the principal targets of genetic damage :-

1- growth-promoting proto-oncogenes.

2- growth-inhibiting tumor suppressor genes.

3- genes that regulate programmed cell death (i.e., apoptosis).

4-genes involved in DNA repair.

1- proto-oncogenes:- are normal cellular counterparts of **oncogenes** . they are physiologic regulators of cell proliferation and differentiation .

Oncogenes they are mutant alleles of **proto-oncogenes** . They are considered dominant because mutation of a single allele can lead to cellular transformation .

2- tumor suppressor genes are genes that normally prevent uncontrolled growth and, when mutated or lost from a cell, allow the transformation to develop .

Retinoblastoma genes (RB) are example of tumor suppressor gene where mutation of these genes leads to transformation by removing the brakes on cell proliferation .

P53.is very important gene called molecular policeman . prevent replication of damaged or faulty DNA cell by

- Cell cycle arrest

- Apoptosis

3- Genes that regulate programmed cell death (i.e., apoptosis).

These genes either prevent programmed cell death (apoptosis) eg . **bcl2** or induced programmed cell death eg. **bax** and **bad** genes

4-Genes involved in DNA repair are those genes that regulate repair of damaged DNA . these affect cell proliferation or survival indirectly by influencing the ability the organism to repair non lethal damage in other genes . A defect in the DNA repair genes can predispose to mutations and hence to neoplastic transformation .

CARCINOGENESIS

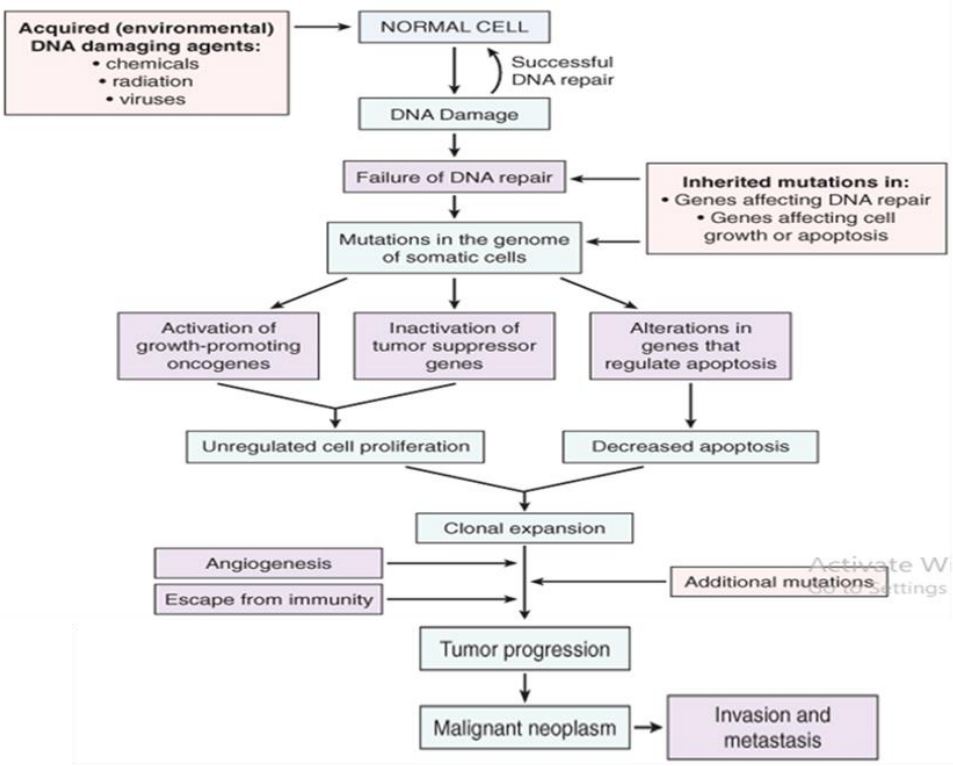
in most instances , no single mutation is sufficient to transform a normal cell in to a cancer cell.

Carcinogenesis is thus a multistep process at both **the phenotypic** and the **genetic** levels, resulting from the accumulation of multiple mutations .

- At phenotypic level excessive growth, local invasiveness & distant metastasis .

many tumors become more aggressive and acquire greater malignant potential. This phenomenon is referred to as **tumor Progression .**

-At genetic (molecular) level, tumor progression result from multiple mutations that accumulate independently in different cells , Some of these mutations may be lethal, but others making the affected cells more adept at growth, survival, invasion, metastasis, or immune evasion . even though most malignant tumors are monoclonal in origin they are genetically heterogeneous .



a simplified scheme of the molecular basis of cancer

Hallmarks of cancer

Eight fundamental changes in cell physiology, which are considered **the hallmarks of cancer** determine phenotypic and biological properties of cancer cells :-

1- Self-sufficiency in growth signals:- the tumor cell have the ability to proliferate without external stimuli , as consequence of oncogene activation .

2-Insensitivity to growth-inhibitory signals :- tumor may not respond to molecules that are inhibitory to the proliferation of normal cells .

3-Evasion of apoptosis:- Caused by mutations in the genes that regulate apoptosis. genes that regulate apoptosis in both normal and cancer cells are **P53** gene is also involved in apoptosis, Overexpression of **BCL2** protein (anti-apoptotic protein) protects tumor cells from apoptosis .

4- Limitless replicative potential:- the tumor cell have unrestricted proliferative capacity

5- Sustained angiogenesis :- Tumors require delivery of oxygen and nutrients and removal of waste products . Malignant tumor stimulate neoangiogenesis by secreting growth factors, such as insulin-like growth factors (IGFs) and platelets derived growth factor PDGF.

6- Ability to invade and metastasize:- A cancer first breach the underlying basement membrane , then traverse the interstitial connective tissue ,and ultimately gain access to the circulation by penetrating the vascular basement membrane .this cycle is repeated when tumor cell emboli extravasate at distant site .

7- Altered cellular metabolism Even in the presence of oxygen, cancer cells have distinctive form of cellular metabolism characterized by high levels of glucose uptake and increased conversion of glucose to lactose via the glycolytic pathway. This phenomenon known as aerobic glycolysis .

8- Evasion of immune surveillance immune surveillance means the immune system is constantly "scan" the body for emerging malignant cells and destroy them .

Host defense against tumors: tumor immunity

Immune surveillance refer to recognition and destruction of non-self tumor cells on their appearance. The strongest evidence for the role of immune surveillance is the increased frequency of cancer in immunodeficient (immunocompromised) host .

Tumor antigens are presented on the cell surface by MHC class I molecules and are recognized by CD8+ CTLs.

Immunocompromised patients have an increased risk of cancer .

In **immunocompetent patients**, tumors may avoid the immune system by several mechanisms, including:-

1- Selection of antigen-negative cells During tumor progression, strongly immunogenic subclones may be eliminated by immune system leaving negative ones , which cannot be detected by immune system .

2-Loss or reduced expression of histocompatibility molecules Tumor cells may not express normal levels of HLA class I molecule , thus escaping attack by CTLs .

3-Immunosuppression Tumors or tumor products also may be immunosuppressive. For example, TGF-β, secreted in large quantities by many tumors, is a potent immunosuppressant .

4- Antigen masking Many tumor cells produce a thicker coat such as **mucopolysaccharides** , than normal cells. This thick coat may block access of immune cells to antigen recognition and cell killing .

5- Downregulation of co-stimulatory molecules . Costimulatory molecules are required to initiate T cell activation. Many tumors reduce these costimulatory molecules .

Effects of Tumor on Host

1-Location is crucial in both benign and malignant tumors. A small (1-cm) pituitary adenoma can compress and destroy the surrounding normal gland and give rise to hypopituitarism. Benign or malignant neoplasms of the gut may causing intestinal obstruction or infarction .

2- Hormone production Adenomas and carcinomas arising in the β-cells of the islets of the pancreas can produce hyperinsulinism , sometimes fatal . some adenomas and carcinomas of the adrenal cortex elaborate corticosteroids e.g., aldosterone, which induces sodium retention , hypertension .

3- bleeding or secondary infection the pressure of benign or malignant tumor on natural surface such as skin , mucosa of GIT may cause ulceration with consequent bleeding or secondary microbial infections .

4- Cancer Cachexia is progressive loss of body weight accompanied by profound weakness , anorexia, and anemia that occur in patient with cancer .it may be due to increase in metabolic rate and reduced food intake and the action of soluble factors such as cytokines produced by the tumor and the host .

5-Paraneoplastic Syndromes is symptom complexes that occur in patients with cancer and that cannot be explained by local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue of origin of the tumor . and it is important to recognize them for several reasons:

A- They may represent the earliest manifestation of an occult neoplasm.

B- In affected patients, the pathologic changes may be associated with significant clinical illness and may even be lethal.

C- They may simulate clinically metastatic disease and confound treatment .

The most common Paraneoplastic syndromes are:-

1- hypercalcemia , hypercalcemia in cancer patients is multifactorial, but the most important mechanism is the synthesis of a parathyroid hormone-related protein by tumor cells.

2- Cushing syndrome Cushing syndrome arising as a paraneoplastic phenomenon usually is related to ectopic production of ACTH or ACTH-like polypeptides by cancer cells, as occurs in small cell cancers of the lung .

3-Hypercoagulability leading to venous thrombosis .

4- Bronchogenic carcinomas may elaborate products identical to or having the same effects of antidiuretic hormone, parathyroid hormone, serotonin, human chorionic gonadotropin, and other bioactive substances .

5-Clubbing of the fingers in patients with lung carcinomas .

Grading and Staging of Cancer

To assess prognosis and effectiveness of treatment .malignant tumor should be determined the degree of differentiation (grade) and extend of cancer spread (stage) because both grade and stage reflect of biological behavior and aggressiveness of neoplasm .

Grading

Is the microscopic feature that explain the behavior of cancer as number of mitosis , presence or absence of foci of necrosis. Cancer are classified to four grades (1-4) i.e. G1 for well differentiated ;G2 for moderately differentiated ; G3 for poorly differentiated and G4 for undifferentiated cancers .

Staging

Staging of cancer depended on

1- Size of primary cancer .

2-Its extent to regional lymph nodes .

3-Presence or absence of blood born metastases .