Etiology of Tumors

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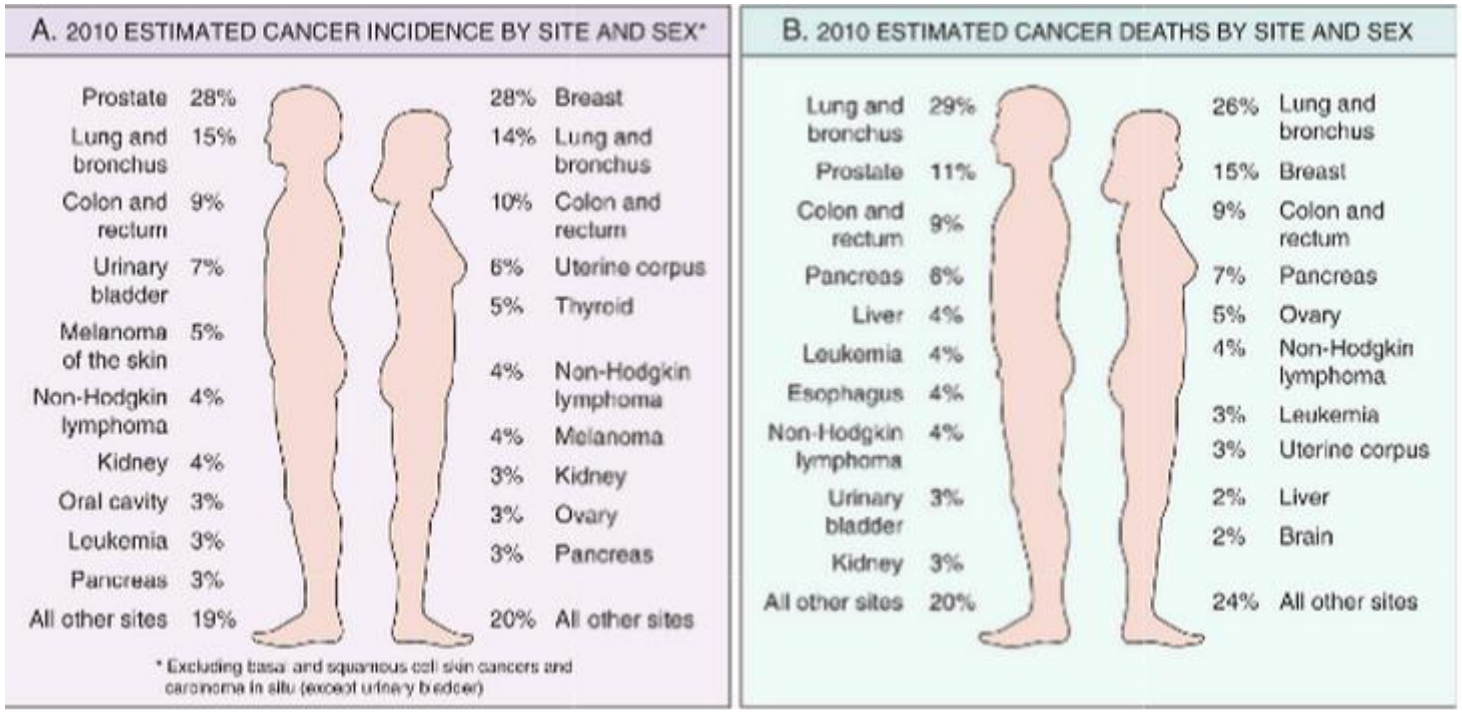
Objectives

- **Understand that incidence of cancer varies with age, race, geographic and genetic factor.**
- **Explain the categories of genetic predisposition to cancer.**
- **Identify the precancerous conditions.**
- **Know the concept of chemical, radiation and microbioloical carcinogenesis.**

Cancer Incidence



- The declining death rate from cervical cancer is directly related to widespread use of cytologic smear studies for early detection of this tumor and its precursor lesions. The development of the human papillomavirus (HPV) vaccine may eliminate this cancer altogether in the coming years.

Geographic and Environmental Variables

- environmental factors are the predominant cause of the most common sporadic cancers.
- For example, death rates from breast cancer are about four to five times higher in the United States and Europe than in Japan. Conversely, the death rate for stomach carcinoma in men and women is about seven times higher in Japan than in the United StatesNearly all the evidence indicates that these geographic differences are environmental rather than genetic in origin.

- Among the possible environmental influences, the most distressing in terms of prevention are those incurred in personal practices, notably cigarette smoking and chronic alcohol consumption.

Agent/Group of Agents	Human Cancer Site and Type for Which Reasonable Evidence Is Available	Typical Use/Occurrence
Arsenic and arsenic compounds	Lung, skin, hemangiosarcoma	Byproduct of metal smelting Component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, mesothelioma; gastrointestinal tract (esophagus, stomach, large intestine)	Formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire-resistant textiles, friction materials (e.g., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Leukemia	Principal component of light oil Many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents Formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung	Missile fuel and space vehicles Hardener for lightweight compounds metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate	Uses include yellow pigments and phosphors Found in solders Used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung	Component of metal alloys, paints, pigments, and preservatives
Ethylene oxide	Leukemia	Ripening agent for fruits and nuts Used in rocket propellant and chemical synthesis, in fumigants for foodstuffs and textiles, and in sterilants for hospital equipment
Nickel compounds	Nose, lung	Nickel plating Component of ferrous alloys, ceramics, and batteries Byproduct of stainless steel arc welding
Radon and its decay products	Lung	From decay of minerals containing uranium Can be serious hazard in quarries and mines
Vinyl chloride	Angiosarcoma, liver	Refrigerant Monomer for vinyl polymers

Age

- In general, the frequency of cancer increases with age. The rising incidence with age may be explained by the accumulation of somatic mutations associated with the emergence of malignant neoplasms . The decline in immune competence that accompanies aging also may be a factor.
- Cancer causes slightly more than 10% of all deaths among children younger than 15 years . The major lethal cancers in children are leukemias, tumors of the central nervous system, lymphomas, and soft tissue and bone sarcomas.

Heredity

- Hereditary forms of cancer can be divided into three categories based on their pattern of inheritance:

1-*Autosomal Dominant Cancer Syndromes*

2-*Autosomal Recessive Syndromes of Defective DNA Repair*

3-*Familial Cancers of Uncertain Inheritance*

- ***Autosomal Dominant Cancer Syndromes***
- Include several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor. The predisposition to these tumors shows an autosomal dominant pattern of inheritance.
- Childhood retinoblastoma is the most striking example of this category. Approximately 40% of retinoblastomas are familial. inherited disabling mutations in a *tumor suppressor gene* are responsible for the development of this tumor in families. Carriers of this gene have a 10,000-fold increased risk of developing retinoblastoma.
- Unlike those with sporadic retinoblastoma, patients with familial retinoblastoma develop bilateral tumors, and they also have a greatly increased risk of developing a second cancer, particularly osteosarcoma.

- *Autosomal Recessive Syndromes of Defective DNA Repair*
- A group of rare autosomal recessive disorders is collectively characterized by chromosomal or DNA instability and high rates of certain cancers. One of the best-studied is xeroderma pigmentosum, in which DNA repair is defective..

- *Familial Cancers of Uncertain Inheritance*
- Virtually all the common types of cancers that occur sporadically have been reported to occur in familial forms where the pattern of inheritance is unclear. Examples are carcinomas of colon, breast, ovary, and brain.
- *Features that characterize familial cancers include early age at onset, tumors arising in two or more close relatives of the index case, and sometimes multiple or bilateral tumors*.
- Familial cancers are not associated with specific marker phenotypes

Table 5–3 Inherited Predisposition to Cancer

Autosomal Dominant Cancer Syndromes	
Gene(s)	**Inherited Predisposition**
RB	Retinoblastoma
TP53	Li-Fraumeni syndrome (various tumors)
p16INK4A	Melanoma
APC	Familial adenomatous polyposis/colon cancer
NF1, NF2	Neurofibromatosis 1 and 2
BRCA1, BRCA2	Breast and ovarian tumors
MEN1, RET	Multiple endocrine neoplasia 1 and 2
MSH2, MLH1, MSH6	Hereditary nonpolyposis colon cancer
PATCH	Nevoid basal cell carcinoma syndrome
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum Ataxia-telangiectasia Bloom syndrome Fanconi anemia	
Familial Cancers of Uncertain Inheritance	
Breast cancer (not linked to *BRCA1* or *BRCA2*) Ovarian cancer Pancreatic cancer	

Acquired Preneoplastic Lesions

- Precursor lesions arise in the setting of chronic tissue injury or inflammation, which may increase the likelihood of malignancy by stimulating continuing regenerative proliferation or by exposing cells to byproducts of inflammation, both of which can lead to somatic mutations .
- Clinically, these precursor lesions are important to recognize, because their removal or reversal may prevent the development of a cancer.
- A brief listing of some of the chief precursor lesions follows:

*Squamous metaplasia and dysplasia of the bronchial mucosa, seen in habitual smokers—a risk factor for lung cancer

*Endometrial hyperplasia and dysplasia, seen in women with unopposed estrogenic stimulation—a risk factor for endometrial carcinoma

*Leukoplakia of the oral cavity, vulva, or penis, which may progress to squamous cell carcinoma

*Villous adenomas of the colon, associated with a high risk of transformation to colorectal carcinoma

ETIOLOGY OF CANCER: CARCINOGENIC AGENTS

- (1) chemicals
- (2) radiant energy
- (3) microbial agents.

- ***Direct-Acting Agents***
- Require no metabolic conversion to become carcinogenic. They are in general weak carcinogens but are important because some of them are cancer chemotherapy drugs (e.g., alkylating agents) used in regimens that may cure certain types of cancer (e.g., Hodgkin lymphoma), only to evoke a subsequent, second form of cancer.
- ***Indirect-Acting* Agents**
- chemicals that require metabolic conversion to an *ultimate carcinogen*. For example, benzo[*a*]pyrene and other carcinogens are formed in the high-temperature combustion of tobacco in cigarette smoking.*These products are implicated in the causation of lung cancer in cigarette smokers*.
- polymorphisms of endogenous enzymes such as cytochrome P-450 may influence carcinogenesis.

Table 5–4 Major Chemical Carcinogens

Direct-Acting Carcinogens
Alkylating Agents
β-Propiolactone
Dimethyl sulfate
Diepoxybutane
Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
Acylating Agents
1-Acetyl-imidazole
Dimethylcarbamyl chloride
Procarcinogens That Require Metabolic Activation
Polycyclic and Heterocyclic Aromatic Hydrocarbons
Benz(*a*)anthracene
Benzo(*a*)pyrene
Dibenz(*a*,*h*)anthracene
3-Methylcholanthrene
7, 12-Dimethylbenz(*a*)anthracene
Aromatic Amines, Amides, Azo Dyes
2-Naphthylamine (β-naphthylamine)
Benzidine
2-Acetylaminofluorene
Dimethylaminoazobenzene (butter yellow)
Natural Plant and Microbial Products
Aflatoxin B_1
Griseofulvin
Cycasin
Safrole
Betel nuts
Others
Nitrosamine and amides
Vinyl chloride, nickel, chromium
Insecticides, fungicides
Polychlorinated biphenyls

Mechanisms of Action of Chemical Carcinogens

- all direct and ultimate carcinogens contain highly reactive electrophile groups that form chemical adducts with DNA, as well as with proteins and RNA. Although any gene may be the target of chemical carcinogens, the commonly mutated oncogenes and tumor suppressors, such as *RAS* and *TP53,* are important targets of chemical carcinogens.
- Carcinogenicity of some chemicals is augmented by subsequent administration of *promoters* (e.g., phorbol esters, hormones, phenols, certain drugs) that by themselves are nontumorigenic. T
- o be effective, repeated or sustained exposure to the promoter must *follow* the application of the mutagenic chemical, or *initiator*.

Radiation Carcinogenesis

- Radiation, whatever its source (UV rays of sunlight, x-rays, nuclear fission, radionuclides) is an established carcinogen
- The oncogenic properties of ionizing radiation are related to its mutagenic effects; it causes chromosome breakage, translocations, and, less frequently, point mutations. Biologically, double-stranded DNA breaks seem to be the most important form of DNA damage caused by radiation.

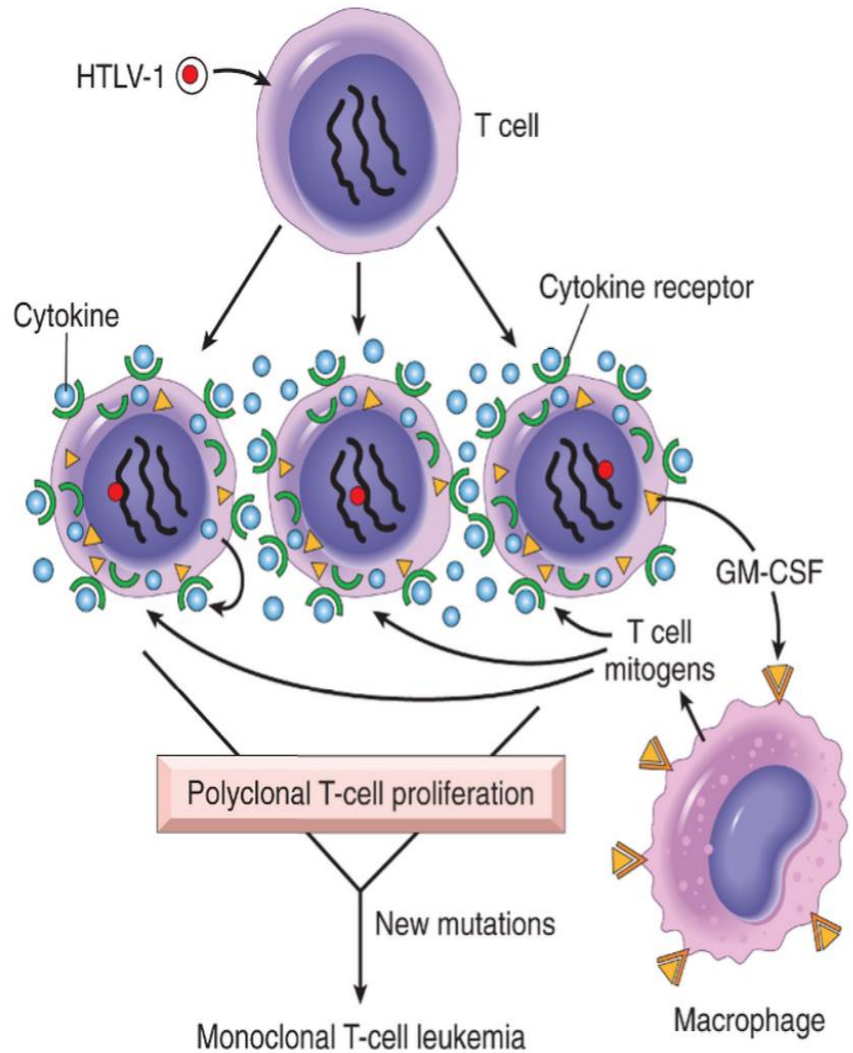
Radiation Carcinogenesis

- Natural UV radiation derived from the sun can cause skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas).
- Of particular relevance to carcinogenesis is the ability to damage DNA by forming pyrimidine dimers. This type of DNA damage is repaired by the nucleotide excision repair pathway. With extensive exposure to UV light, the repair systems may be overwhelmed, and skin cancer results.
- Inherited disease *xeroderma pigmentosum* have a defect in the nucleotide excision repair pathway. As expected, there is a greatly increased predisposition to skin cancers in this disorder.

Viral and Microbial Oncogenesis

- Oncogenic RNA viruses:
- HTLV-1 is associated with a form of T cell leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean basin but is found sporadically elsewhere.
- HTLV-1 has tropism for CD4+ T cells, and this subset of T cells is the major target for neoplastic transformation. Human infection requires transmission of infected T cells through sexual intercourse, blood products, or breastfeeding. Leukemia develops only in about 3% to 5% of infected persons after a long latent period of 20 to 50 years.

- The HTLV-1 genome encodes a viral TAX protein, which turns on genes for cytokines and their receptors in infected T cells. This sets up autocrine and paracrine signaling loops that stimulate T cell proliferation. Although this proliferation initially is polyclonal, the proliferating T cells are at increased risk for secondary mutations that lead to the outgrowth of a monoclonal leukemia.


HTLV-1
T cell
Cytokine
Cytokine receptor
GM-CSF
T cell
mitogens
Polyclonal T-cell proliferation
New mutations
Monoclonal T-cell leukemia
Macrophage

- Oncogenic DNA Viruses:
- Four DNA viruses :HPV, Epstein-Barr virus (EBV), Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8 [HHV-8]), and hepatitis B virus (HBV)—are strongly associated with human cancer.

Human Papillomavirus

- HPV is associated with benign warts (Low risk HPV e.g types 6 &11), as well as cervical cancer (High risk HPV e.g types 16&18).
- The oncogenicity of HPV is related to the expression of two viral oncoproteins, E6 and E7; they bind to Rb and p53, respectively, neutralizing their function.
- E6 and E7 from high-risk strains of HPV (which give rise to cancers) have higher affinity for their targets than do E6 and E7 from low-risk strains of HPV (which give rise to benign warts).

Epstein-Barr Virus

- EBV is implicated in the pathogenesis of a diverse list of tumors, including Burkitt's lymphoma, B cell lymphomas in patients with defective T cell immunity (e.g., those infected with HIV), a subset of Hodgkin lymphoma, nasopharyngeal carcinoma, a subset of T cell lymphomas, gastric carcinomas, NK cell lymphomas, and even, in rare instances, sarcomas, mainly in the immunosuppressed.
- Burkitt lymphoma is endemic in certain parts of Africa and is sporadic elsewhere.
- Certain EBV gene products contribute to oncogenesis by stimulating a normal B cell proliferation pathway. Concomitant compromise of immune competence allows sustained B cell proliferation, leading eventually to development of lymphoma, with occurrence of additional mutations such as t(8;14) leading to activation of the *MYC* gene.

Hepatitis B and Hepatitis C Viruses

- Between 70% and 85% of hepatocellular carcinomas worldwide are due to infection with HBV or HCV.
- The oncogenic effects of HBV and HCV are multifactorial, but the dominant effect seems to be immunologically mediated chronic inflammation, with hepatocellular injury, stimulation of hepatocyte proliferation, and production of reactive oxygen species that can damage DNA.
- The HBx protein of HBV and the HCV core protein can activate a variety of signal transduction pathways that also may contribute to carcinogenesis.

Helicobacter pylori

- *H. pylori* infection has been implicated in both gastric adenocarcinoma and MALT lymphoma.
- The mechanism of *H. pylori*–induced gastric cancers is multifactorial, including immunologically mediated chronic inflammation, stimulation of gastric cell proliferation, and production of reactive oxygen species that damage DNA. *H. pylori* pathogenicity genes, such as *CagA,* also may contribute by stimulating growth factor pathways.
- It is thought that *H. pylori* infection leads to polyclonal B cell proliferations and that eventually a monoclonal B cell tumor (MALT lymphoma) emerges as a result of accumulation of mutations.

Summary

- The incidence of cancer varies with age, race, geographic factors and genetic background. Most cancers are sporadic but some are familial. Predisposition to hereditary cancers may be autosomal dominant or autosomal recessive. Some acquired disease (pre-neoplastic disorders) are known to be associated with an increased risk of cancer.
- Three classes of carcinogenic agents have been identified:
- Chemicals.
- Radiation.
- Viral and Microbial agents.