EPIDEMIOLOGY AND ETIOLOGY OF TUMORS

Dr. Maria A. Arafah

Associate Professor – Department of Pathology

http://fac.ksu.edu.sa/mariaarafah/courses

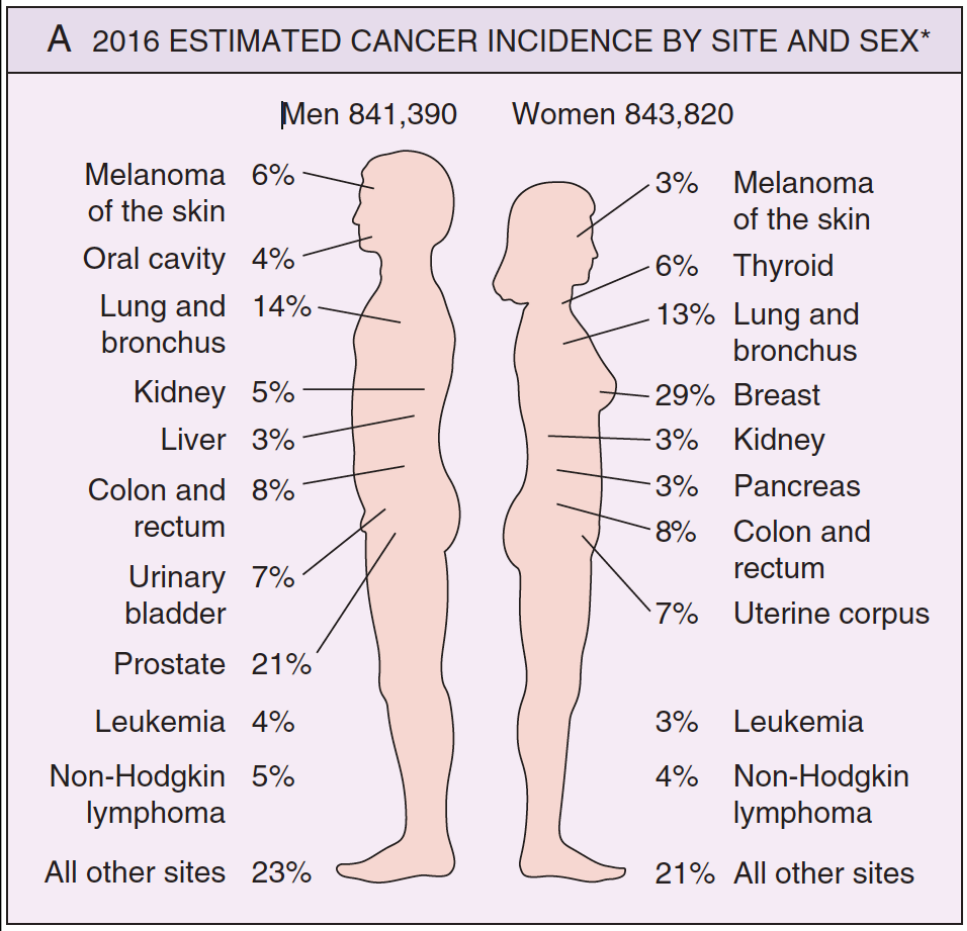
Objectives

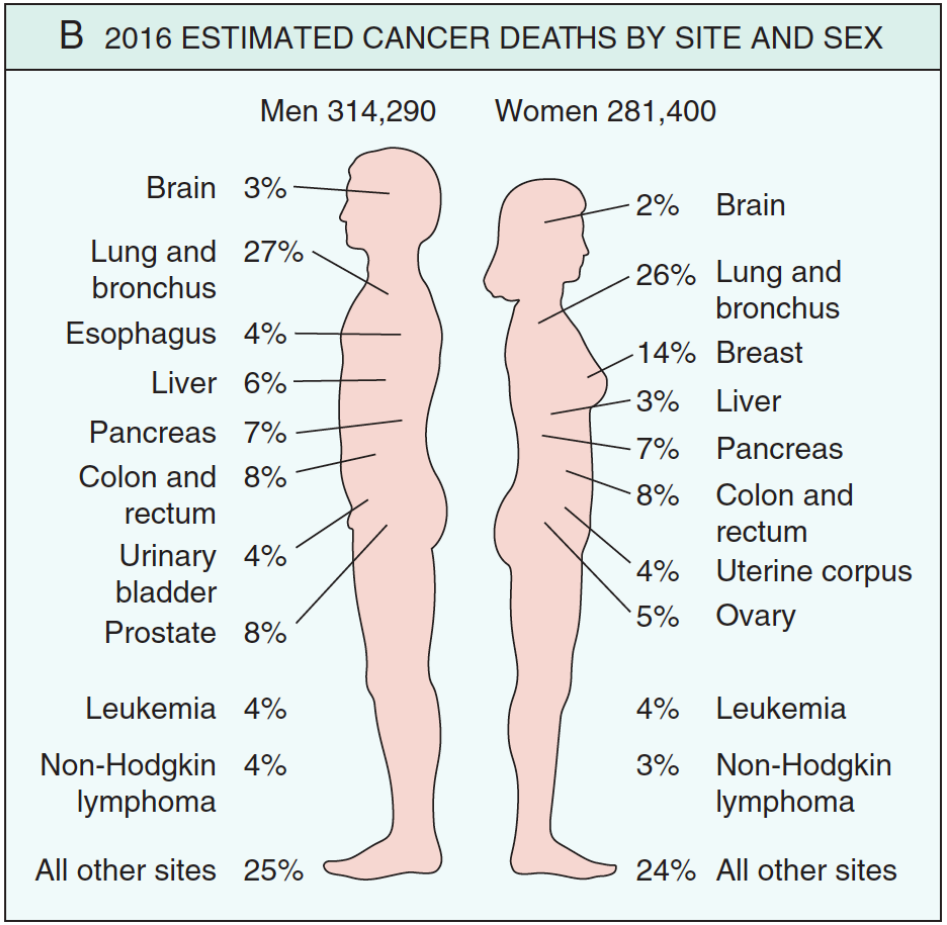
- To understand that the incidence of cancer varies with age, race, geographic and genetic factors.
- To explain the genetic predisposition to cancer.
- To identify the precancerous conditions.
- To list the various causes of tumors.

Epidemiology

- Studying the epidemiology of tumors will aid in the following:
  - Discover etiologic factors
  - Plan preventive measures
  - Know what types of tumors are common and what are rare
  - Develop screening methods for early diagnosis

Cancer Incidence





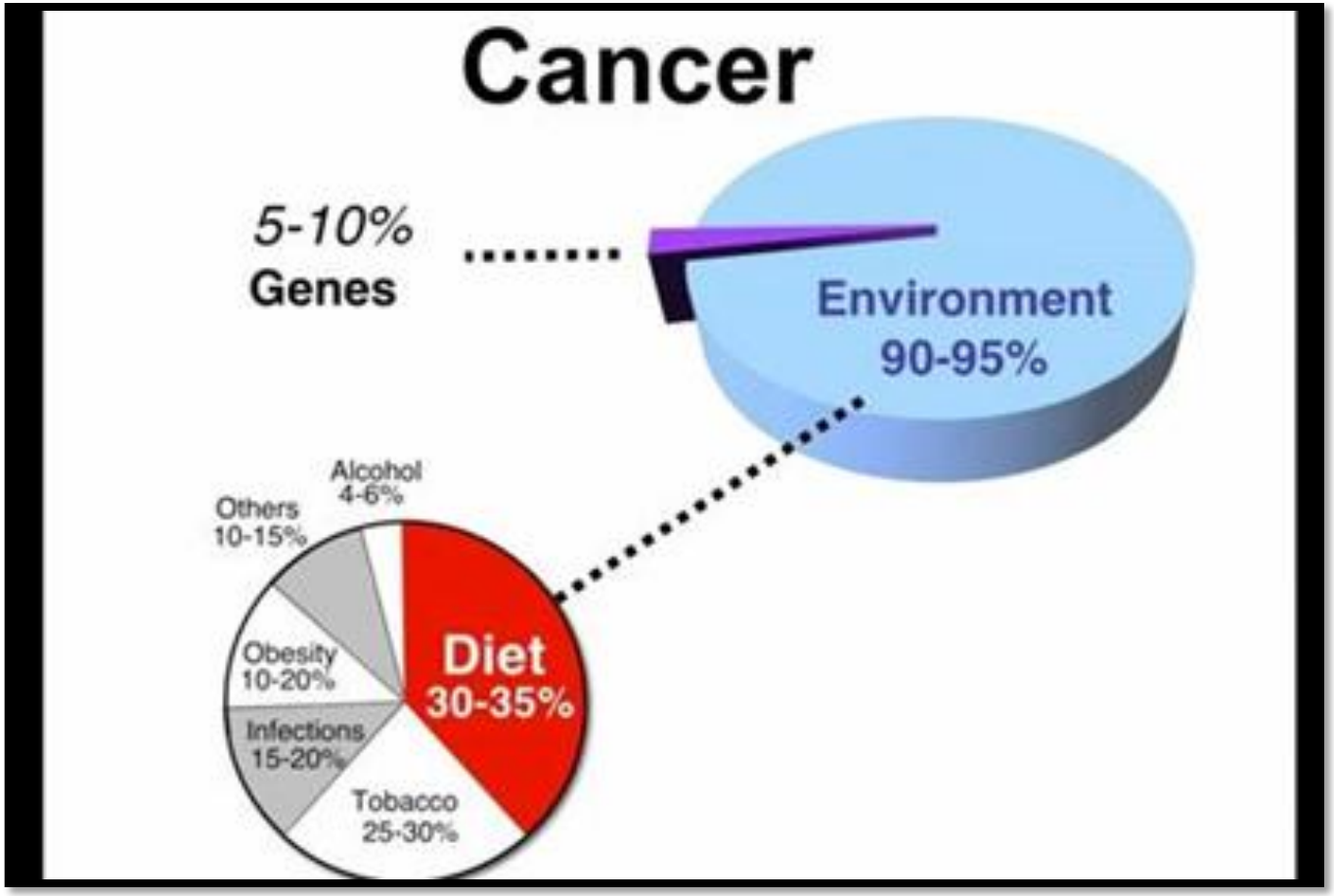
Cancer Incidence

- Factors affecting the incidence of cancer:
  - Geographic and environmental factors
  - Age
  - Hereditary factors
  - Acquired preneoplastic conditions

Geographic & Environmental Factors

- The rate of gastric carcinoma in Japan is 7 times its rate in North America & Europe.
- The rate of breast carcinoma in North America is 5 times its rate in Japan.
- Liver cell carcinoma is more common in African populations.

Geographic & Environmental Factors



Geographic & Environmental Factors

- Exposure to asbestos → mesothelioma
- Smoking → lung carcinoma
- Multiple sexual partners → cervical carcinoma
- Fat-rich diet → colon carcinoma

Geographic & Environmental Factors

Table 6.2 Occupational Cancers

Agents or Groups of Agents	Human Cancers for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Arsenic and arsenic compounds	Lung carcinoma, skin carcinoma	By-product of metal smelting; component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, esophageal, gastric, and colon carcinoma; mesothelioma	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 (i.e., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Acute myeloid leukemia	Principal component of light oil; despite known risk, 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 carcinoma	Missile fuel and space vehicles; hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate carcinoma	Uses include yellow pigments and phosphors; found in solders; used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung carcinoma	Component of metal alloys, paints, pigments, and preservatives
Nickel compounds	Lung and oropharyngeal carcinoma	Nickel plating; component of ferrous alloys, ceramics, and batteries; by-product of stainless-steel arc welding
Radon and its decay products	Lung carcinoma	From decay of minerals containing uranium; potentially serious hazard in quarries and underground mines
Vinyl chloride	Hepatic angiosarcoma	Refrigerant; monomer for vinyl polymers; adhesive for plastics; formerly inert aerosol propellant in pressurized containers

Age

- Generally, the frequency of cancer increases with age.
- Most cancer mortality occurs between 55 and 75 years of age and it also increases during childhood.
- The most common malignant tumors in children are:
  - Leukemia
  - CNS tumors
  - Lymphomas
  - Soft tissue & bone sarcomas.

Hereditary Factors

- Hereditary factors include:
  - Autosomal dominant cancer syndromes
  - Autosomal recessive syndromes of defective DNA repair
  - Familial cancers of uncertain inheritance

Hereditary Factors

- Autosomal dominant cancer syndromes
  - Several well-defined cancers in which inheritance of a single mutant gene greatly increases the risk of developing a tumor.
  - e.g. retinoblastoma in children:
    - 40% of retinoblastomas are familial in nature.
    - Carriers of this mutation have 10000 fold increase in the risk of developing retinoblastoma
  - e.g. multiple endocrine neoplasia (MEN syndrome)

Hereditary Factors

- 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.
  - e.g. xeroderma pigmentosum

Hereditary Factors

- Familial cancers of uncertain inheritance
  - All the common types of cancers that occur sporadically have been reported to occur in familial forms where the pattern of inheritance is unclear.
  - e.g. breast, colon, ovary, brain
  - Familial cancers usually have unique features:
    - They start at early age
    - They are multiple or bilateral
    - They occur in two or more relatives

Hereditary Factors

Table 6.4 Inherited Predisposition to Cancer

Inherited Predisposition	Gene(s)
Autosomal Dominant Cancer Syndromes	
Retinoblastoma	*RB*
Li-Fraumeni syndrome (various tumors)	*TP53*
Melanoma	*CDKN2A*
Familial adenomatous polyposis/colon cancer	*APC*
Neurofibromatosis 1 and 2	*NF1, NF2*
Breast and ovarian tumors	*BRCA1, BRCA2*
Multiple endocrine neoplasia 1 and 2	*MEN1, RET*
Hereditary nonpolyposis colon cancer	*MSH2, MLH1, MSH6*
Nevoid basal cell carcinoma syndrome	*PTCH1*
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum	Diverse genes involved in nucleotide excision repair
Ataxia-telangiectasia	*ATM*
Bloom syndrome	*BLM*
Fanconi anemia	Diverse genes involved in repair of DNA cross-links

Acquired Pre-neoplastic Conditions

- Acquired preneoplastic conditions are conditions that predispose to cancer.
  - Dysplastic bronchial mucosa in smokers→ lung carcinoma
  - Liver cirrhosis → liver cell carcinoma
  - Margins of chronic skin fistulae → squamous cell carcinoma
  - Endometrial hyperplasia → endometrial carcinoma
  - Leukoplakia of the oral cavity, vulva or penis → squamous cell carcinoma
  - Villous adenoma of the colon or rectum → colorectal adenocarcinoma

Acquired Pre-neoplastic Conditions

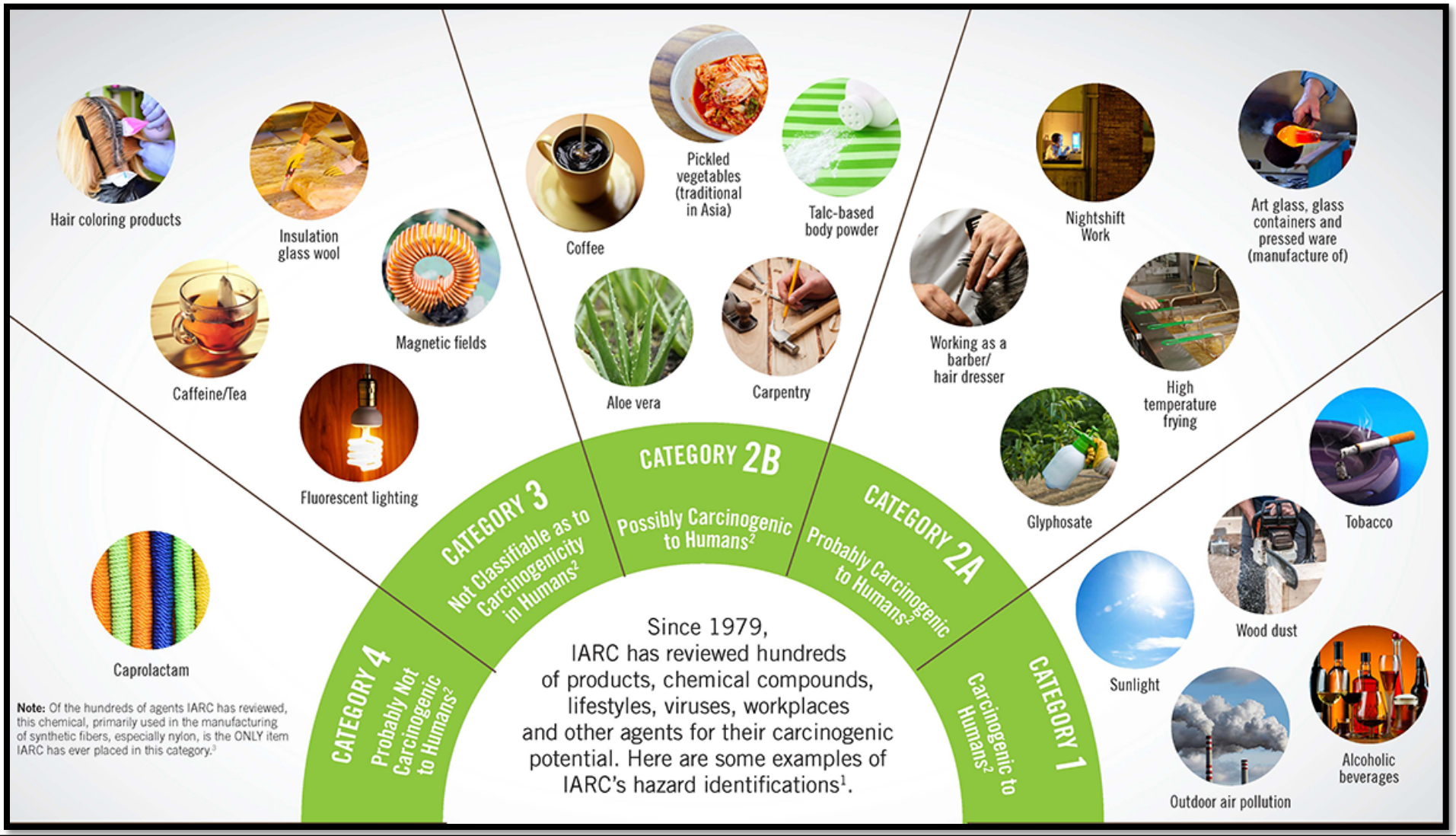
Table 6.3 Chronic Inflammatory States and Cancer

Pathologic Condition	Associated Neoplasm(s)	Etiologic Agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibers, silica particles
Inflammatory bowel disease	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell carcinoma	
Pancreatitis	Pancreatic carcinoma	Alcoholism, germ line mutations (e.g., in the trypsinogen gene)
Chronic cholecystitis	Gallbladder cancer	Bile acids, bacteria, gallbladder stones
Reflux esophagitis, Barrett esophagus	Esophageal carcinoma	Gastric acid
Sjögren syndrome, Hashimoto thyroiditis	MALT lymphoma	
Opisthorchis, cholangitis	Cholangiocarcinoma, colon carcinoma	Liver flukes *(Opisthorchis viverrini)*
Gastritis/ulcers	Gastric adenocarcinoma, MALT lymphoma	*Helicobacter pylori*
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Chronic cervicitis	Cervical carcinoma	Human papillomavirus
Chronic cystitis	Bladder carcinoma	Schistosomiasis

Etiology of Tumors

- Classes of carcinogenic agents:
  - Chemicals
  - Radiant energy
  - Microbial agents

Etiology of Tumors



Chemical Carcinogens

- Chemical carcinogens can be natural or synthetic.
- They can cause cellular damage via:
  - Direct
  - Indirect

Chemical Carcinogens

- Direct-acting agents
  - They 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).

Chemical Carcinogens

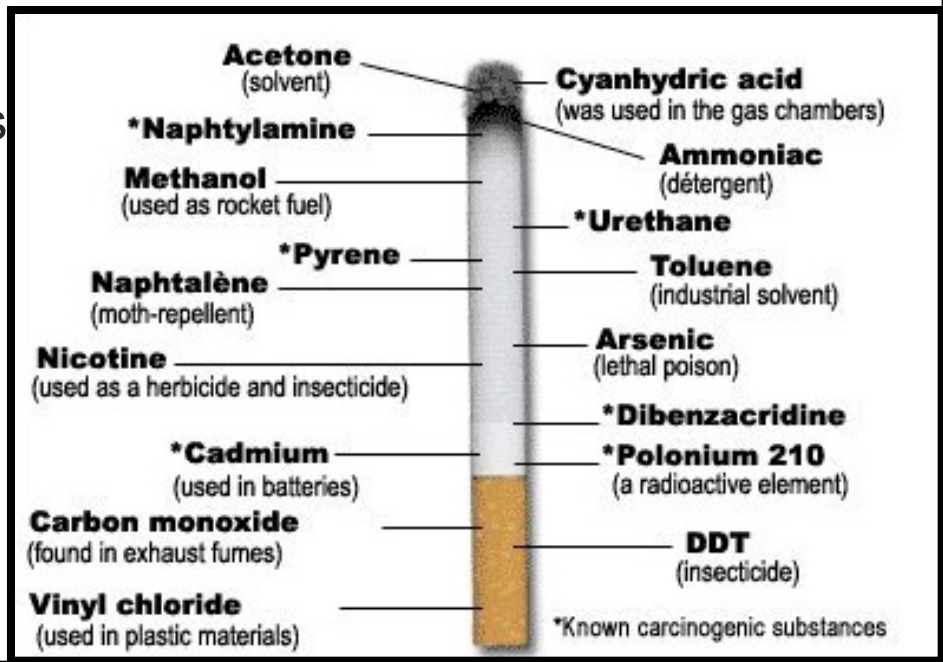
- Indirect-acting agents
  - They require metabolic conversion of the chemical compound (*procarcinogen*) to active & carcinogenic products (*ultimate carcinogen*).
  - e.g. benzo[*a*]pyrene, aromatic amines, azo dyes & Aflatoxin B_1

Chemical Carcinogens

- Mechanisms of action:
  - Most chemical carcinogens are mutagenic i.e. cause genetic mutations.
    - the commonly mutated oncogenes & tumor suppressors are *RAS* and *TP53.*
  - All direct chemical carcinogens & ultimate chemical carcinogens are highly reactive as they have electron-deficient atoms.
  - They react with the electron rich atoms in the RNA, DNA & other cellular proteins.

Chemical Carcinogens

- Alkylating agents
- Polycyclic hydrocarbons
  - Cigarette smoking
  - Animal fats during broiling meats
  - Smoked meats & fish



Chemical Carcinogens

- Aromatic amines & azo dyes:
  - B-naphthylamine cause bladder cancer in rubber industries & aniline dye.
  - Some azo dyes, used to color food, cause bladder cancer.

Chemical Carcinogens

- Nitrosamines & nitrosamides are used are preservatives & cause gastric carcinoma.

- Alfatoxin B_1, produced by Aspergillus which grow on improperly stored grains, it causes hepatocellular carcinoma.

Chemical Carcinogens

Table 6.5 Major Chemical Carcinogens

Direct-Acting Carcinogens
Alkylating Agents
β-Propiolactone
Dimethyl sulfate
Diepoxybutane
Anti-cancer 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

Radiation

- Radiation, whatever its source (UV rays of sunlight, x-rays, nuclear fission, radionuclides) is an established carcinogen.

- Radiation has mutagenic effects: chromosomes breakage, translocations & point mutations.

Radiation

- UV rays of sunlight
  - It causes skin cancers: melanoma, squamous cell carcinoma & basal cell carcinoma.
  - It is capable of DNA damage & mutations of p53 tumor suppressor gene.
  - When extensive exposure to UV rays occurs, the repair system is overwhelmed → skin cancer.

Viral & Microbial Oncogenes

- Viral & microbial oncogenes include:
  - RNA viruses
  - DNA viruses
  - Other micro-organisms e.g. H. Pylori bacteria

Viral & Microbial Oncogenes

- Host cells have endogenous gene to maintain a normal cell cycle.
- Oncogene viruses induce cellular proliferation, mimic or block cellular signals necessary for the cell cycle regulation.

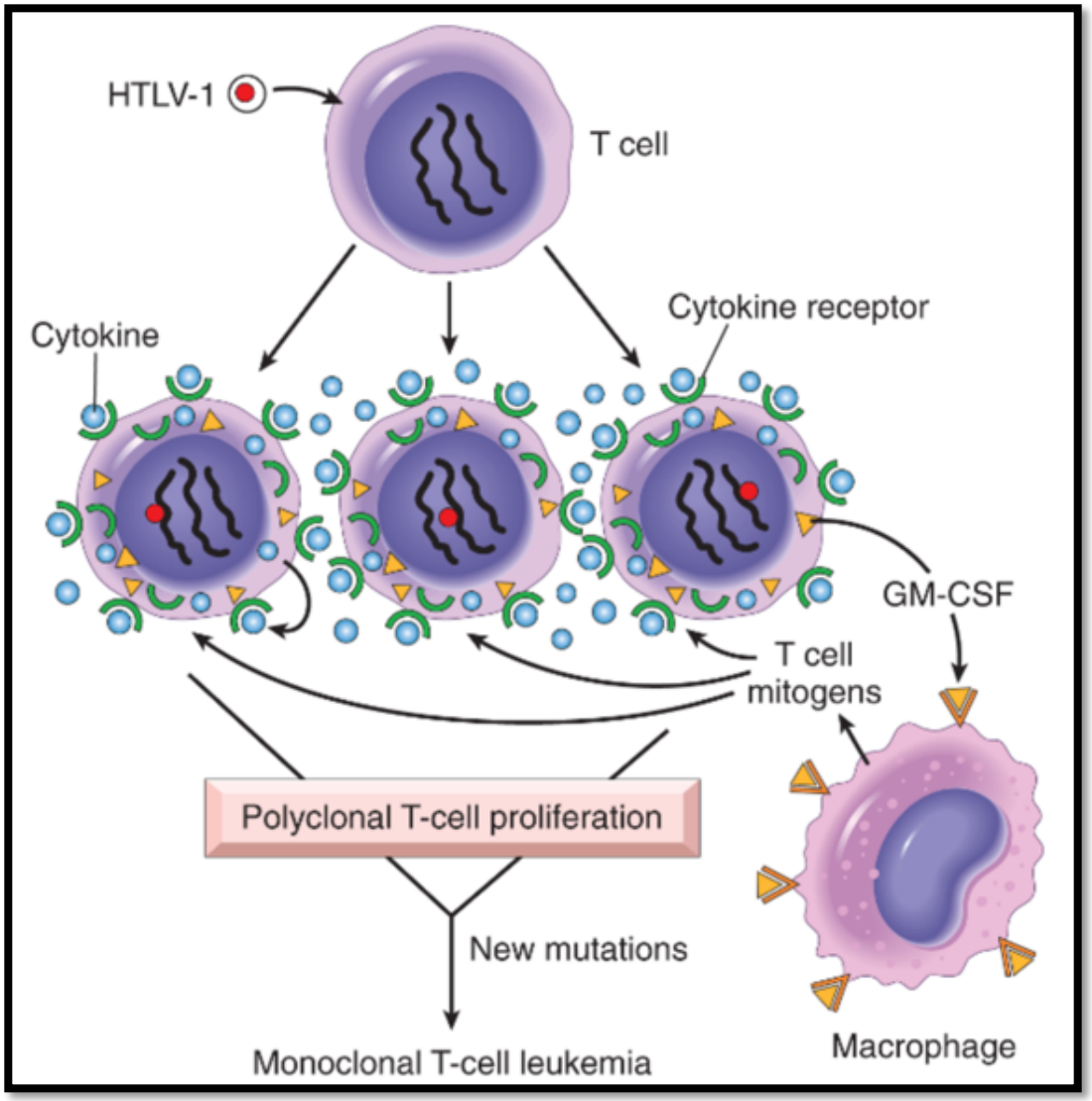
Viral & Microbial Oncogenes

- RNA oncogenic viruses:
  - Human T cell lymphotropic virus-1 (HTLV-1), a retrovirus, infects & transforms T-lymphocytes.
  - It causes T-Cell leukemia/Lymphoma after a prolonged latent period (20-30 years).
  - It is endemic in Japan & the Caribbean.

Viral & Microbial Oncogenes

- RNA oncogenic viruses:
  - It is transmitted like HIV but only 1% of infected patients develop T-cell leukemia/Lymphoma.
  - No cure or vaccine to HTLV-1.
  - Treatment: chemotherapy with common relapses.

HTLV-1 Infection



Viral & Microbial Oncogenes

- DNA oncogenic viruses:
  - DNA viruses form stable associations with hosts DNA, thus the transcribed viral DNA transforms the host cells.
  - e.g.
    - Human papilloma virus (HPV)
    - Epstein Barr virus (EBV)
    - Hepatitis B virus (HBV)
    - Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8 [HHV-8])

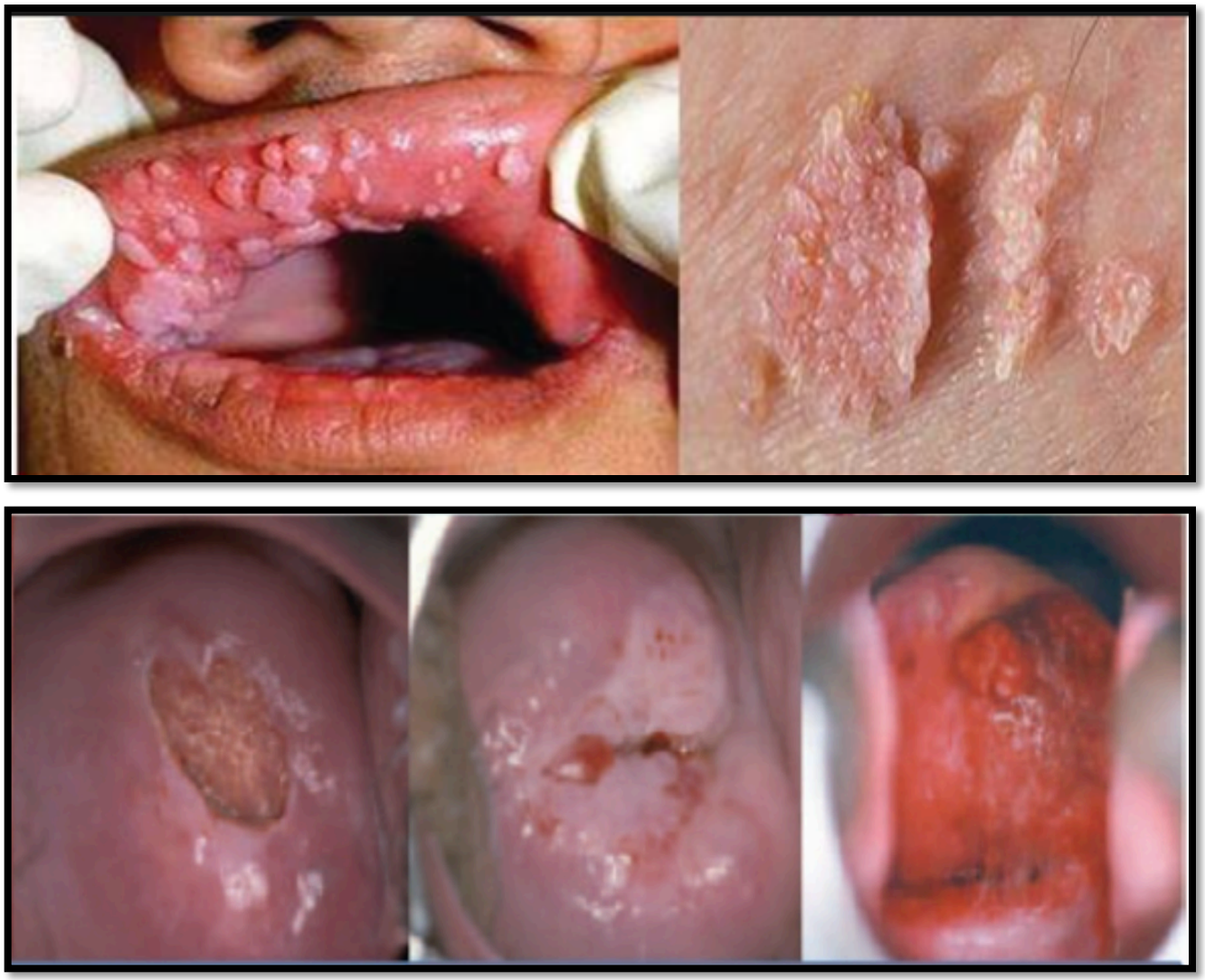
Viral & Microbial Oncogenes

- HPV infection:
  - HPV has more than 70 serotypes.
  - It is a sexually transmitted.
  - It causes benign warts, squamous cell carcinoma of the cervix, anogenital region, mouth & larynx.

Viral & Microbial Oncogenes

- HPV infection:
  - HPV types 6 and 11:
    - Genital warts
  - HPV types 16, 18, 31:
    - 85% of cervical carcinomas are caused by HPV 16 or 18
    - High risk HPV types integrates with the host's DNA

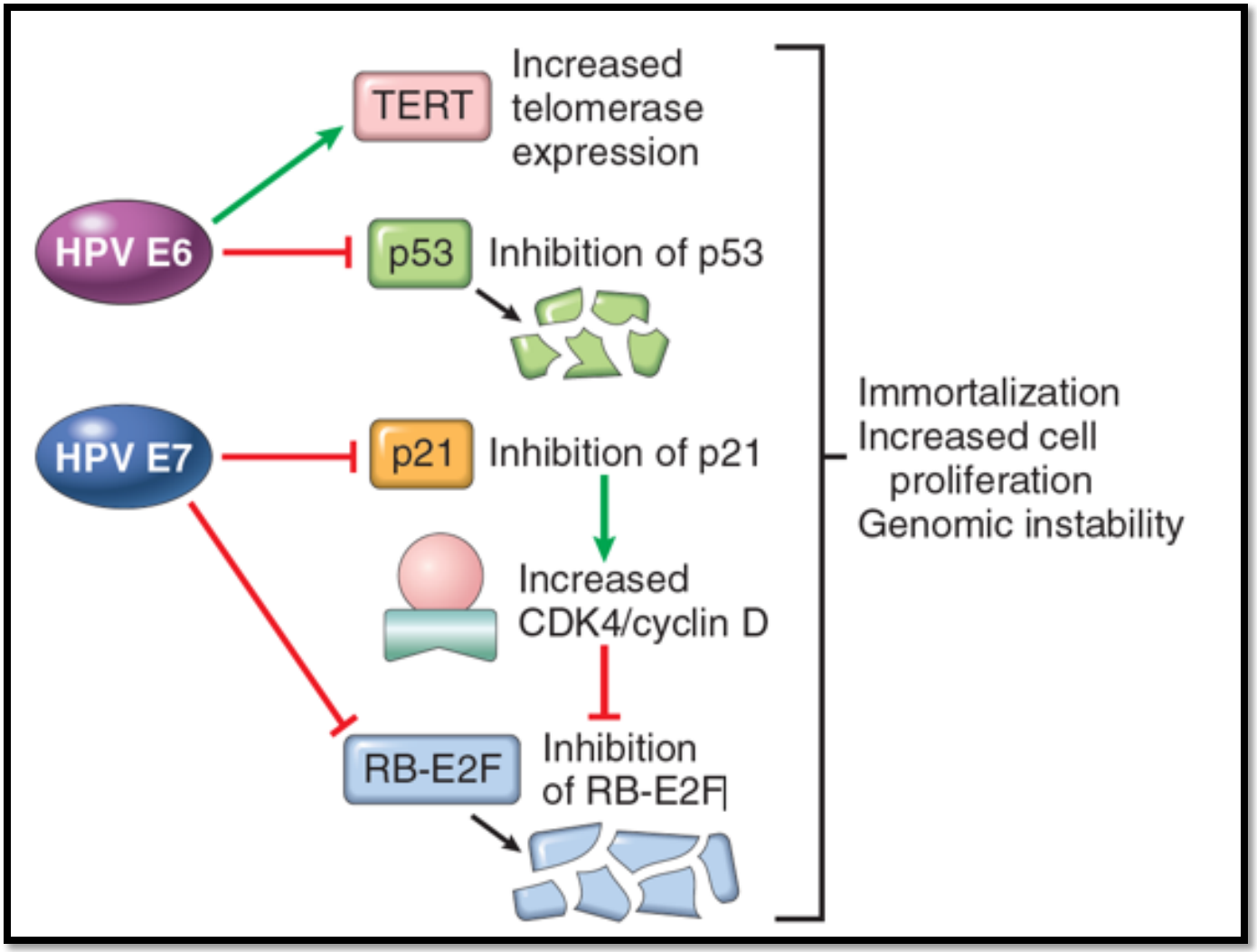
HPV Infection



Viral & Microbial Oncogenes

- HPV infection:
  - The oncogenic potential of HPV 16 and 18 can be related to products of two early viral genes, E6 and E7.
  - E7 protein binds to Rb tumor suppressor and releases the E2F transcription factors that normally are sequestered by Rb, promoting progression through the cell cycle.
  - E6 protein binds to p53 & facilitates its degradation.

HPV infection



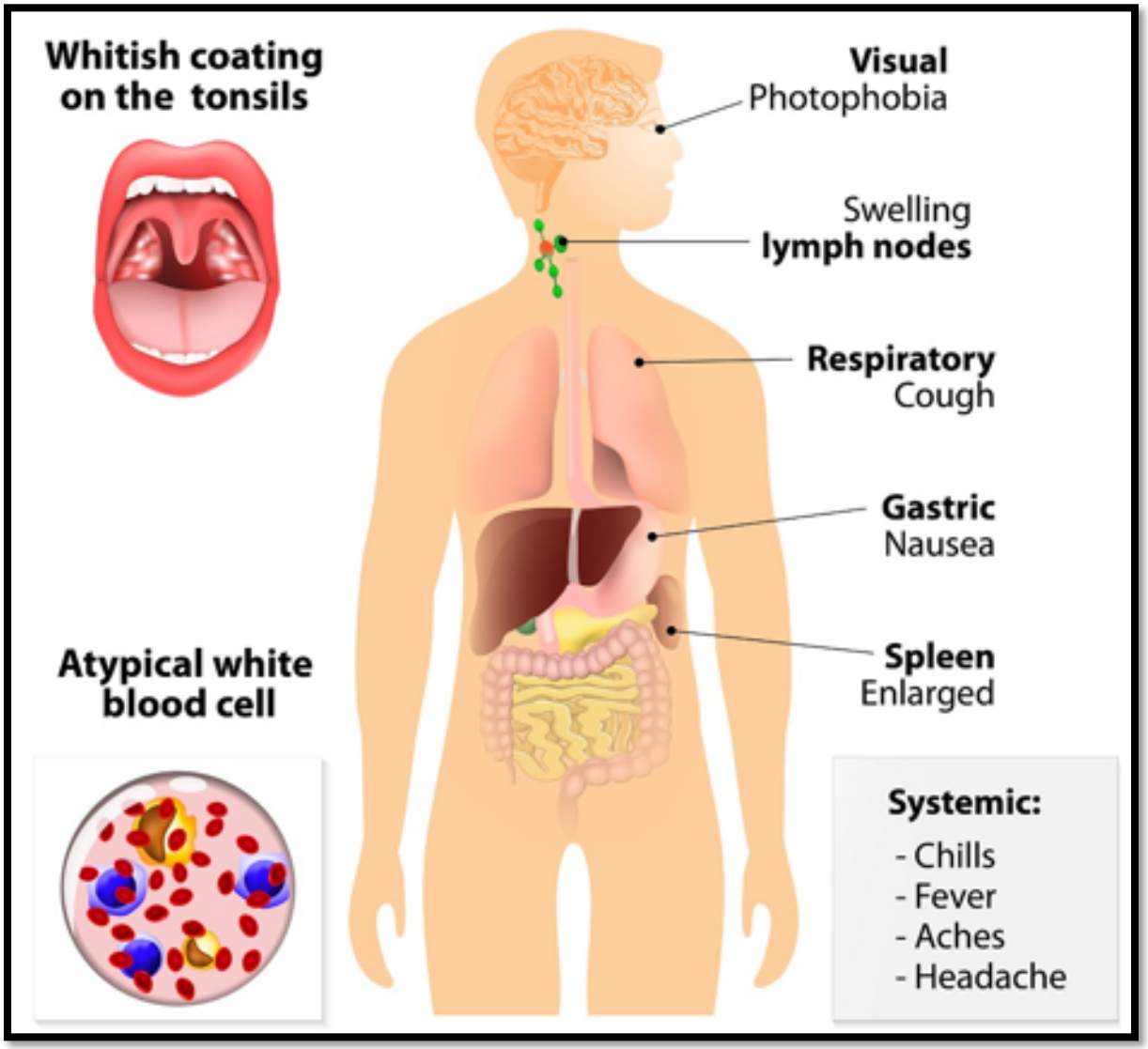
Viral & Microbial Oncogenes

- HPV infection:
  - HPV infection alone is not sufficient to cause carcinoma and other factors also contribute to the development of cervical carcinoma e.g.
    - cigarette smoking
    - coexisting infections
    - hormonal changes

Viral & Microbial Oncogenes

- EBV infection:
  - It is a common virus worldwide.
  - It infects B lymphocytes & epithelial cells of the nasopharynx.
  - It causes infectious mononucleosis.
  - It causes several malignant tumors e.g.
    - Burkitt's Lymphoma
    - B-cell lymphoma in immunosuppressed
    - Nasopharyngeal carcinoma

EBV Infection – Infectious Mononucleoses



Viral & Microbial Oncogenes

- EBV infection:
  - Nasopharyngeal carcinoma is a malignant neoplasm arising from the nasopharygeal epithelium.
  - It is endemic in South China and parts of Africa.
  - 100% of cases contain EBV genome in these endemic areas.

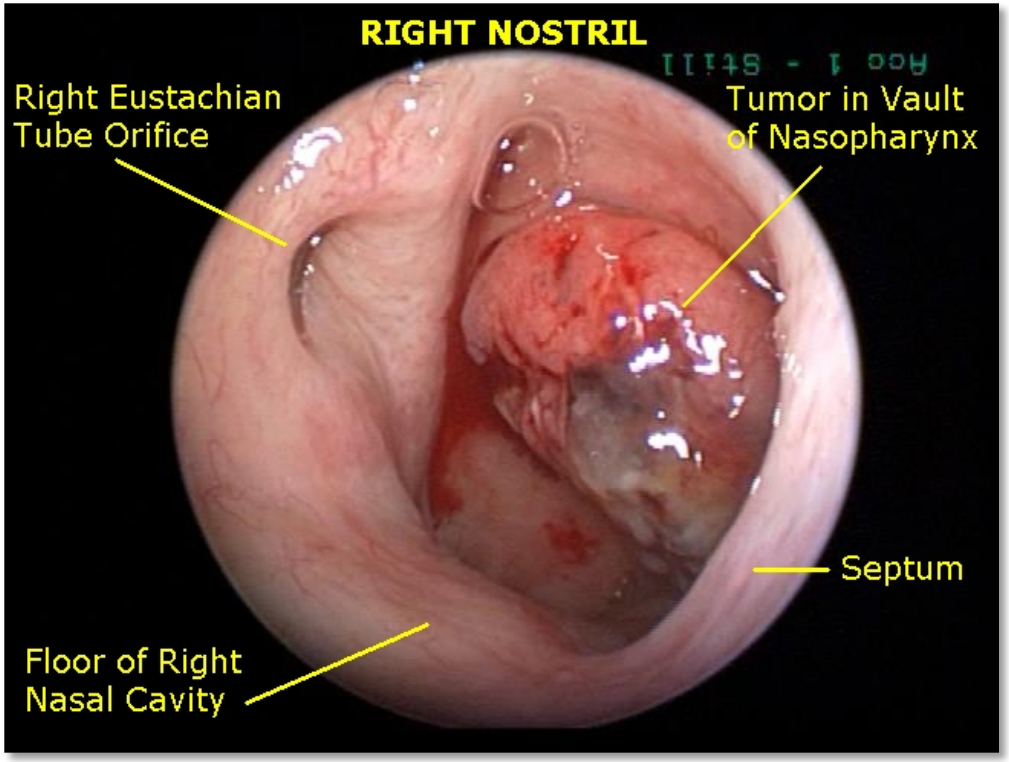
Viral & Microbial Oncogenes

- EBV infection:
  - EBV also causes Burkitt's lymphoma, a highly malignant B-cell tumor.
  - However, rare sporadic cases occur worldwide.
  - EBV-related Burkitt's lymphoma is the most common childhood tumor in Africa.
  - All cases have t(8:14) genetic mutation.

Viral & Microbial Oncogenes

- EBV infection:
  - EBV causes B lymphocyte cellular proliferation.
  - It causes loss of growth regulation.
  - It predisposes the cells to genetic mutations, especially t(8:14).

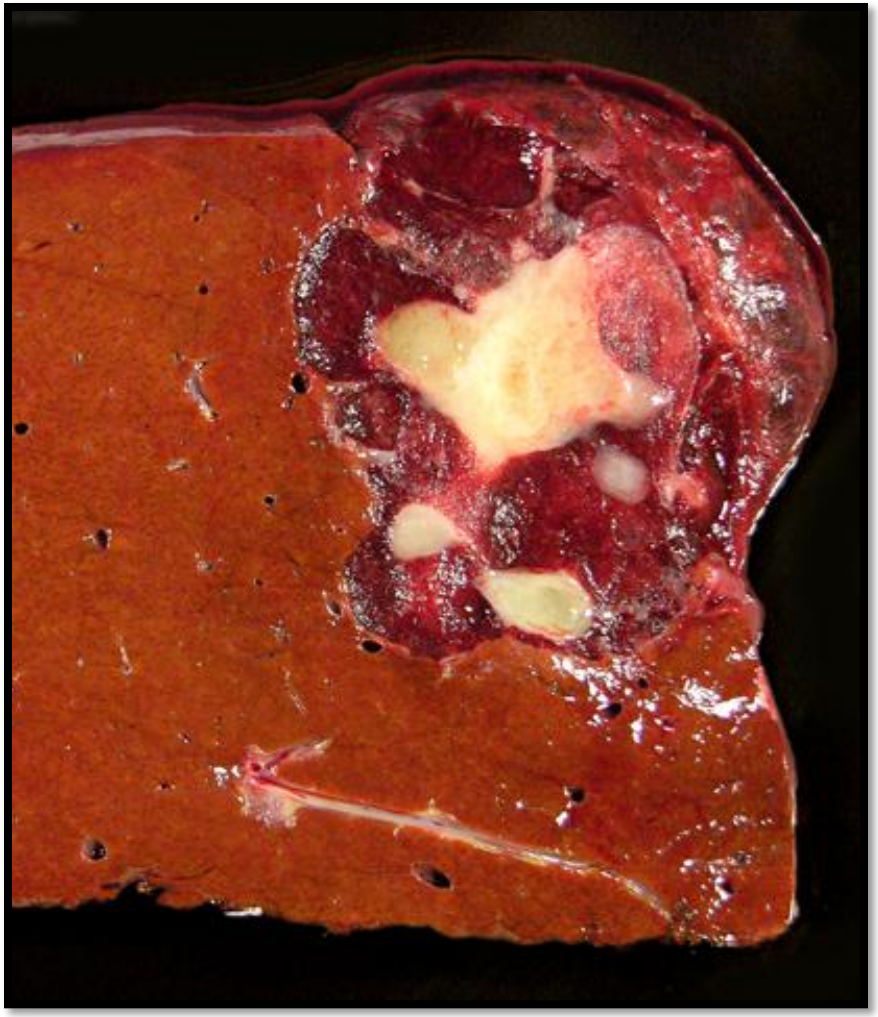
EBV Infection

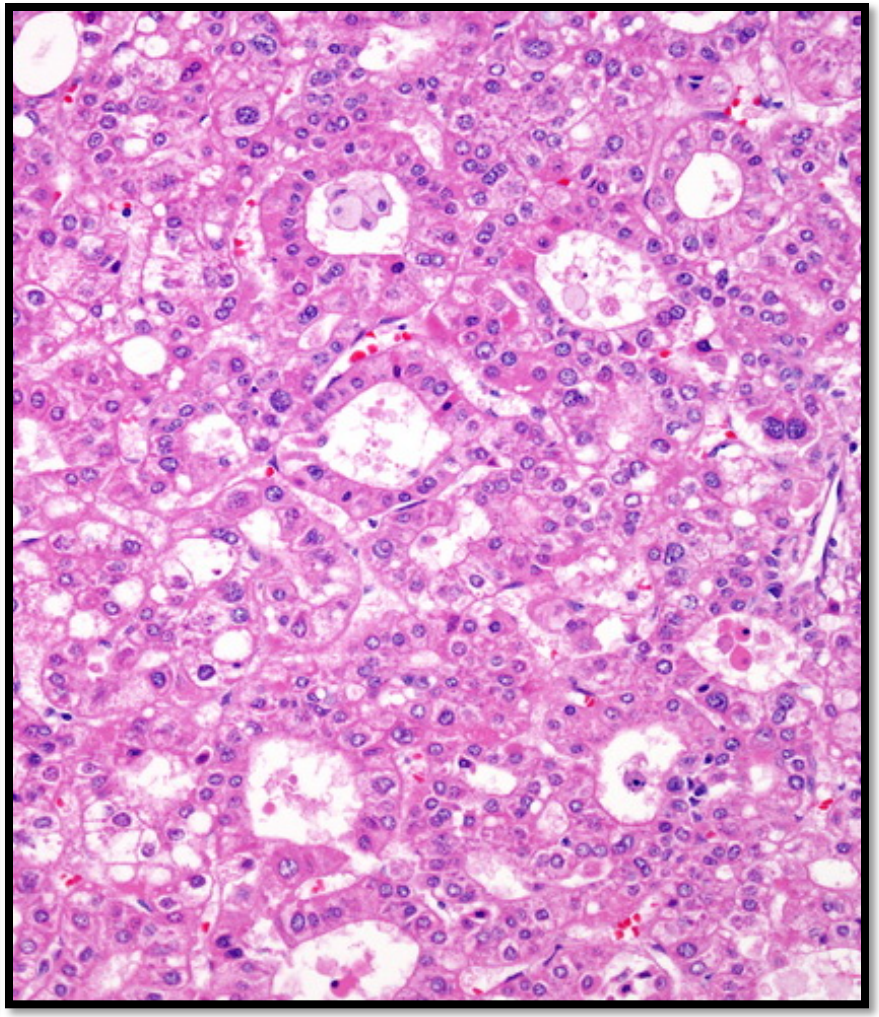


Viral & Microbial Oncogenes

- HBV infection:
  - HBV infection has a strong association with liver cell carcinoma (HCC).
  - It is present world-wide, but most commonly in the far East & Africa.
  - HBV infection incurs up to 200-fold risk of HCC.

HBV Infection

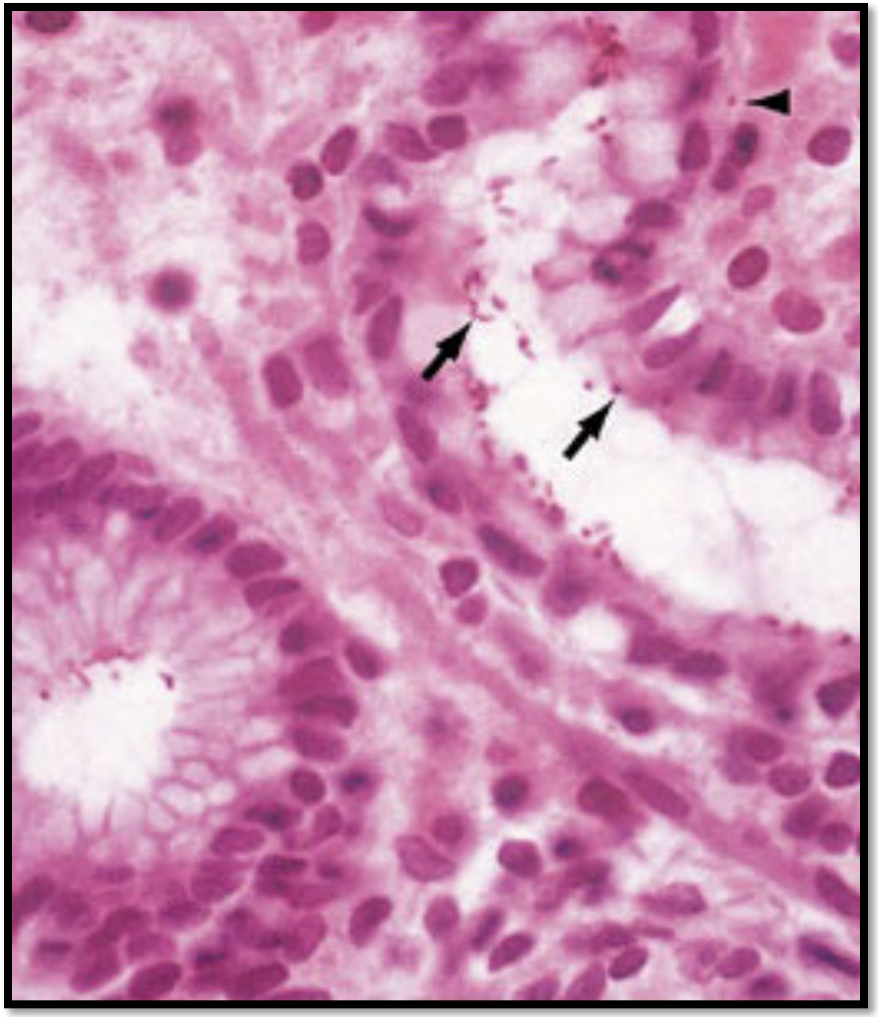


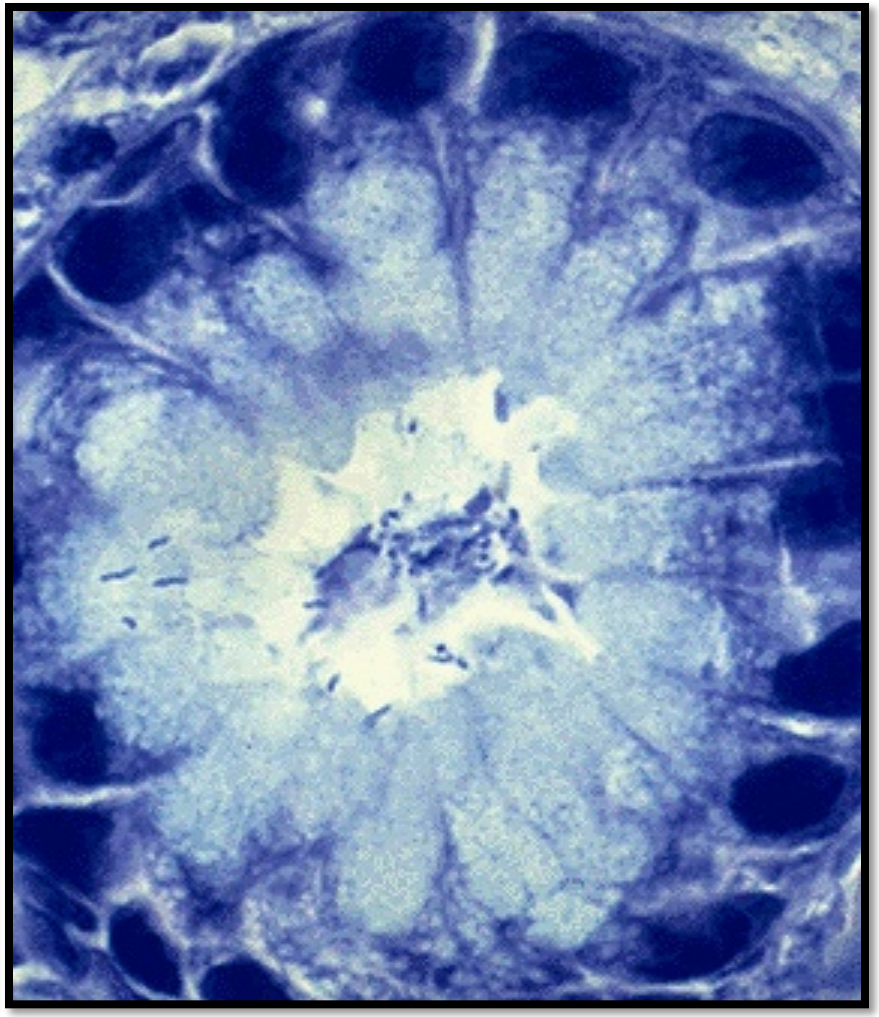


Viral & Microbial Oncogenes

- Helicobacter Pylori bacteria:
  - It is bacteria that infects the stomach
  - It causes:
    - Peptic ulcers
    - Gastric lymphoma (Mucosal Associated Lymphoid Tumor (MALT)
    - Gastric carcinoma

H. Pylori Infection





Reference

- Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 10th ed. Elsevier; 2018. Philadelphia, PA.

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Thank You